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Asymmetric Dearomatization/Cyclization Enables Access to Polycyclic Chemotypes

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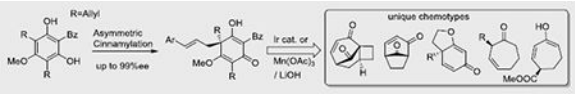
Abstract

Enantioenriched, polycyclic compounds were obtained from a simple acylphloroglucinol scaffold. Highly enantioselective dearomatization was accomplished using a Trost ligand-palladium(0) complex. A computational DFT model was developed to rationalize observed enantioselectivities and revealed a key reactant-ligand hydrogen bonding interaction. Dearomatized products were used in visible light-mediated photocycloadditions and oxidative free radical cyclizations to obtain novel polycyclic chemotypes including tricyclo[4.3.1.$0^{1,4}$]decan-10-ones, bicyclo[3.2.1]octan-8-ones and highly-substituted cycloheptanones.

Abstract



Enantioenriched, polycyclic compounds were obtained from a simple acylphloroglucinol scaffold. Highly enantioselective dearomatization was accomplished using a Trost ligand- palladium(0) complex. Dearomatized products were used in visible light-mediated photocycloadditions and oxidative free radical cyclizations to obtain novel polycyclic chemotypes.

Keywords

asymmetric catalysis; dearomatization; photocatalysis; polycycles; radical reactions

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Dedicated to Professor Stuart L. Schreiber on the occasion of his 60th birthday

Introduction

Polyprenylated polycyclic acylphloroglucinols (PPAPs) are a natural product class well-known for their diverse biological activities,[1] and their complex structures have attracted the attention of many chemists in the field of natural product total synthesis.[2] We have previously shown that dearomative alkylation at the 6-position of 4,6-diallyl-2-benzoyl-5-*O*-methyl-phloroglucinol (**1**) enables the synthesis of PPAPs such as 7-*epi*-nemorosone (**2**)[3] and plukenetione A (**3**)[4] (Figure 1).

Diversity-oriented synthesis (DOS) enables the assembly of small molecule screening libraries with high sp^3 carbon and chiral center content for use in drug discovery.[5][6] In order to access complex compound libraries in minimal steps from simple starting materials, the development of efficient, complexity-generating synthetic methodology is critical. Herein, we report a new strategy for generation of enantioenriched, polycyclic compounds *via* two-step dearomatization/cyclization sequences. Asymmetric, dearomative cinnamylation of simple benzoyl phloroglucinol **1** produces chemotype **4** bearing multiple olefinic functional handles that can be exploited for subsequent intramolecular cyclizations to produce novel polycyclic chemotypes (Figure 2).

Results and Discussion

We first evaluated dearomative, asymmetric cinnamylation[7] of substrate **1** using Trost ligand-Pd^0 complexes (Table 1). Treatment of **1** with cinnamyl carbonate **5a**, (*S,S*)-DACH-phenyl Trost ligand (**L1**), Cs_2CO_3, and $Pd_2(dba)_3$[8] afforded the cinnamylated product **4a** in 72% yield and 99 % *ee* (Entry 1). The absolute stereochemistry of **4a** was determined by X-ray crystallography of the derived *p*-bromobenzoate **6a** (Figure 3).[9] Use of (*R,R*)-DACH-phenyl Trost ligand (**L2**) afforded the opposite enantiomer (***ent*-4a,** *not shown*) in 81% yield (Entry 2). The DPEDA-type Trost ligand **L3** gave a slightly lower yield and % *ee* than was observed with **L1** (Entry 3). (*S,S*)-DACH-naphthyl ligand (**L4**) was not effective for the reaction (Entry 4). Use of the (*S,S*)-ANDEN-phenyl type ligand (**L5**) provided the opposite enantiomer in 44% yield and 24 % *ee* (Entry 5).

We next investigated substrate scope (Table 2). Both naphthyl- (**5b**) and 4-bromophenyl-substituted (**5c**) substrates were well tolerated. Reactions of carbonates with electron-donating groups such as 4-methoxyphenyl (**5d**) or 2-furanyl (**5e**) were more sluggish, requiring 48 h for full consumption of **1**. Enantiopurities of the products (**4b-e**) were high (91-99 % *ee*). Conversely, 4-nitrophenyl substrate (**5f**) showed only moderate enantioselectivity. Altering the substitution at the allylic double bond completely prevented the reaction (**g** and **h**).

Our provisional model to rationalize enantioselectivity is depicted in Figure 4. For Tsuji-Trost allylic alkylations involving prochiral **π**-allyl complexes, a wall/flap cartoon mnemonic aids in predicting stereochemical outcomes.[10] This model has also been used to predict the facial discrimination of simple prochiral enolates.[10b-d] Lloyd-Jones, Norrby, and coworkers have reported computational and NMR studies indicating that, in contrast to the C_2-symmetric geometry assumed in the wall/flap model, experimental evidence suggests

that the allyl group is situated remotely from the DACH ligand in a complex that is not symmetric on the NMR timescale.[11] Given the complexity of **1** and the asymmetry of the cinnamyl cation, we relied on computational modeling with DFT-optimized **L1**-Pd-η3-cinnamyl complexes using the Lloyd-Jones/Norrby geometry. DFT optimizations of pro-*R* and pro-*S* outer-sphere approaches of the naked anion of **1** (a hydrogen-bond stabilized exocyclic enolate)[12] in toluene indicated that for each input complex, the pro-*R* (observed) approach was energetically favored.[13] In the lowest-energy complex, **L1** participates in a hydrogen bond with **1**, as well as a π-stacking interaction with the cinnamyl cation. A similar hydrogen bond was observed in Lloyd-Jones' transition state calculations of cesium malonate with an **L2**-Pd-η3-allyl complex, giving rise to a quasi-inner sphere transition state wherein enantioselectivity is governed by pre-coordination of the nucleophile to the ligand rather than the Pd atom.[14]

With enantioenriched dearomatized cores bearing multiple olefinic moieties in hand, we next pursued oxidative cyclization reactions as a strategy to rapidly generate structural complexity. We first explored visible light photoredox catalysis.[15] Knowles and coworkers have shown that visible light catalysts can generate heteroatom radicals by proton-coupled electron transfer (PCET), and that the radicals may be trapped by alkenes to access heterocycles.[16] Inspired by this approach, we postulated that the enol **4** may be an excellent substrate for radical generation at the 2-position, with subsequent trapping by the pendant cinnamyl group.

In the event, compound **4a** was converted to three different chemotypes on treatment with $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ ("Ir catalyst") under blue LED irradiation (Table 3, Entry 1). After detailed NMR analysis, it was determined that the expected photoredox product (**9a**) was produced in 11% yield, as well as tricycles **7a** and **8a** in 22% and 13% yields, respectively. These compounds presumably arise *via* [2+2] photocyclization (De Mayo reaction)[17] between the styrenyl alkene and *exo*-enol, with the Ir catalyst serving as photosensitizer.[18] In contrast, 2-naphthyl enol (**4b**) did not afford **8b** and **9b**, presumably due to steric hindrance (Entry 2). The 4-bromophenyl (**4c**) and 4-nitrophenyl (**4e**) substrates were slow to react (Entries 2 and 5). 4-Methoxyphenyl-substituted **4d** reacted smoothly with a product distribution similar to that observed with **4a**.

Subsequent *in situ* NMR experiments indicated that prior to cyclization to **7a**/**8a**, clean photoisomerization of the styrene of **4a** occurs, suggestive of triplet energy transfer. Identical *E*/*Z* ratios were obtained irrespective of the starting isomer (Scheme 1). Based on these observations, a mechanistic proposal for the formation of [2+2]-cycloadducts and the cyclization product **9a** is shown in Scheme 2. First, the styrenyl moiety (*ca.* 60 kcal/mol triplet energy)[17a] is sensitized by the visible light-excited Ir catalyst (61 kcal/mol triplet energy).[11a] The *exo*-enol is then excited through intramolecular triplet energy transfer from the excited styrene and reacts *via* [2+2] cycloaddition with the *trans*-cinnamyl group to afford compounds **7a** and **8a**. The conformer enabling [2+2] cycloaddition with the *cis*-cinnamyl substrate is likely disfavored due to allylic strain. Instead, *cis*-cinnamyl isomer **4a′** is converted to [3.2.1]-bicycle **9a** *via* a redox process.

In order to further probe the intramolecular reactivity of **4**, we also investigated oxidative free radical cyclization using $Mn(OAc)_3/Cu(OAc)_2$.[19] While treatment with Mn^{III} and Cu^{II} gave intractable mixtures, treatment of **4a** with $Mn(OAc)_3$ in acetic acid produced acetate **10a** in 19% yield (Table 4, Entry 1). Scheme 3 depicts a proposed mechanism. The radical generated at the 2-position cyclizes with the cinnamyl group positioned to minimize torsional strain with the benzoyl group in the 5-centered transition state. The resultant benzyl radical may undergo one electron oxidation by Mn^{III} to afford a benzylic cation, stabilized as the oxonium by the adjacent benzoyl carbonyl, which may be trapped by acetic acid with stereochemical inversion to afford **10a**. 4-Bromophenyl derivative **4c** similarly gave **10c** (Entry 2). A competing pathway, in which the cinnamyl alkene undergoes *5-exo-trig* cyclization with the 1-*O*-radical, was observed with 4-methoxy-substituted substrate **4d**. We propose that the electron-donating group enables further Mn^{III}-mediated oxidation of the resultant benzylic radical to a stabilized benzyl cation which may then trapped by acetate to form **11** (Entry 3).[13]

We next explored further reactivity of the dearomatization/cyclization-derived polycycles. First, [3.2.1]-bicycle **10a** was treated with LiOH in methanol to give the highly substituted 7-membered ester **12a** *via* a retro-Dieckmann process (Scheme 4A). Compound **7a** was subjected to similar conditions, producing decarbonylated cycloheptanone **13a** as a single diastereomer in 53% yield (Scheme 4B). Next, compound **7a** was treated with the non-nucleophilic base NaH. Under these conditions, bicyclo-[3.2.1] derivative **14a** was obtained in 20% yield along with 22% of recovered **7a**. This product may presumably be obtained *via* protonation of an *anti*-Bredt enolate carbanion[20] after retro-aldol cleavage of the cyclobutanol. [3.2.1]-Bicycle **14a** was converted to **13a** in 38% yield upon LiOH treatment (Scheme 5). We propose that the one-pot conversion of **7a** to **13a** may also arise *via* a retro-aldol–retro-Dieckmann sequence. Alternatively, a mechanism in which retro-Dieckmann fragmentation precedes retro-aldol reaction may be operative. In either case, the retro-Dieckmann fragmentation for **14a** occurs orthogonally to that observed for **10a**, presumably due to the absence of a benzoyl group stabilizing the resulting anion.

Conclusions

In summary, we have established a new strategy for generating unique enantioenriched mono- and polycyclic chemotypes. Highly enantioselective cinnamylation of a phloroglucinol scaffold provided dearomatized substrates which were converted by divergent cyclizations to structures including tricyclo[4.3.1.$0^{1,4}$]decan-10-ones and bicyclo[3.2.1]heptanones. The polycyclic chemotypes were ring-opened to afford highly substituted 7-membered products. Preliminary computational studies indicated the potential for interesting pre-organizing intramolecular interactions between the ligand/Pd^0/substrate complex and the incoming enolate nucleophile. Studies exploring further intramolecular transformations of the dearomatized scaffolds, as well as rigorous computational examination of the asymmetric allylic alkylation using transition state calculations, are currently in progress and will be reported in due course.

Experimental Section

Full experimental details for the preparation of the compounds described herein, as well as details related to computational and mechanistic experiments, are provided in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. CCDC 1487867 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via*www.ccdc.cam.ac.uk/data_request/cif
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20. Hayes CJ, Simpkins NS. Org Biomol Chem. 2013; 11:8458. [PubMed: 24202405]

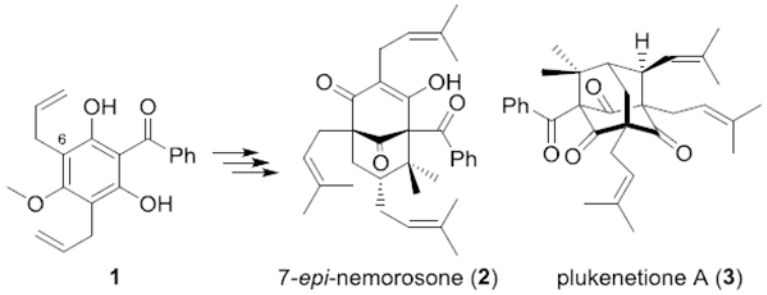


Figure 1.
Natural products derived from acylphloroglucinol scaffold **1**

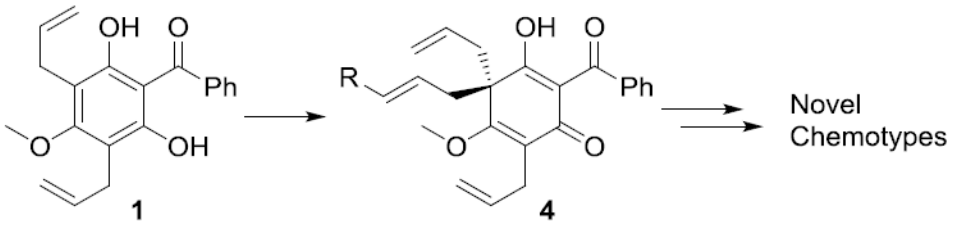


Figure 2.
Asymmetric cinnamylation of **1** and further cyclizations of **4** gives rise to novel chemotypes

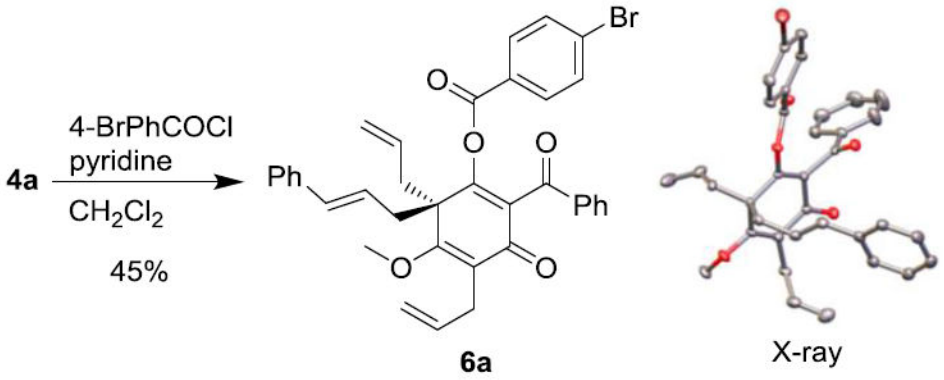


Figure 3.
Determination of absolute stereochemistry of *p*-bromobenzoate **6a**

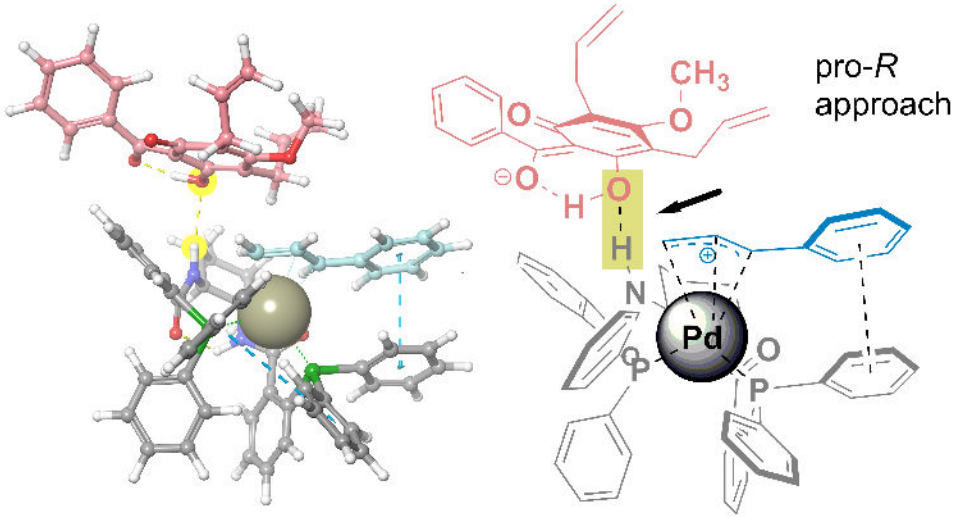
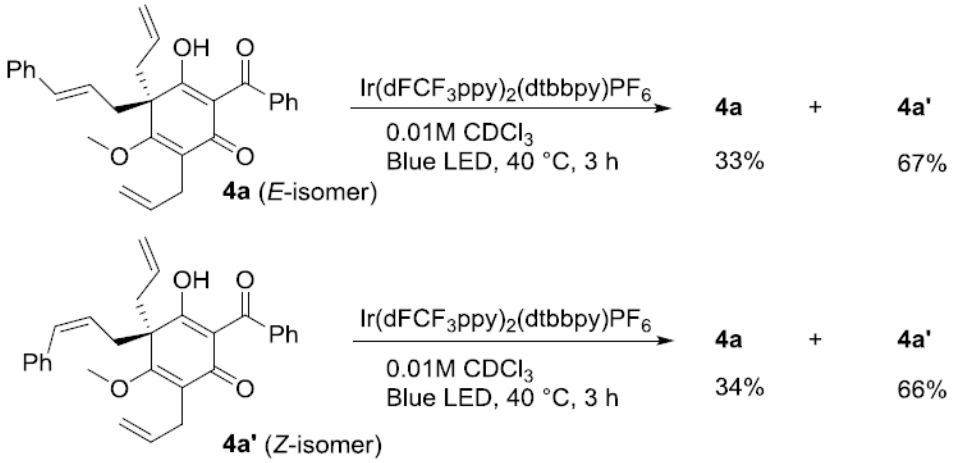


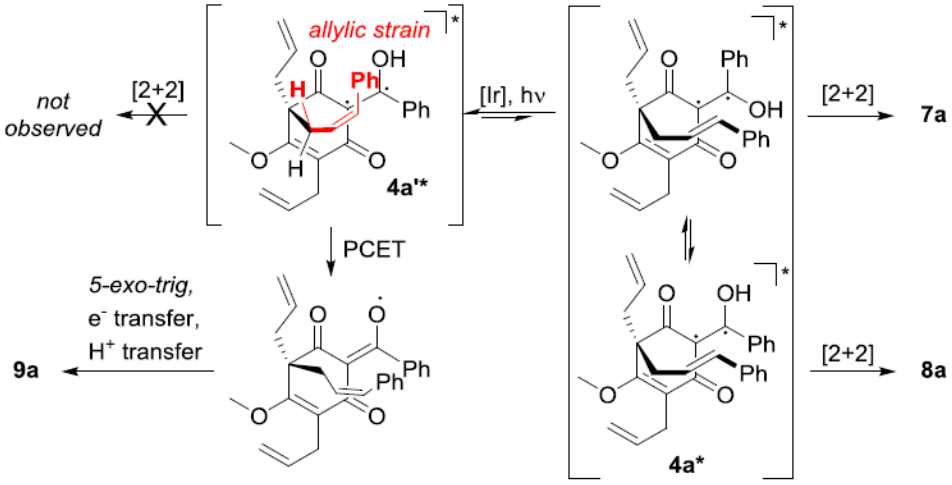
Figure 4.

DFT-optimized (B3LYP-LACV3P**++) structure (Schrödinger's Jaguar) of the lowest-energy **L1**-Pd-η3-cinnamyl-enolate approach indicating a hydrogen bond between the incoming enolate and ligand N-H



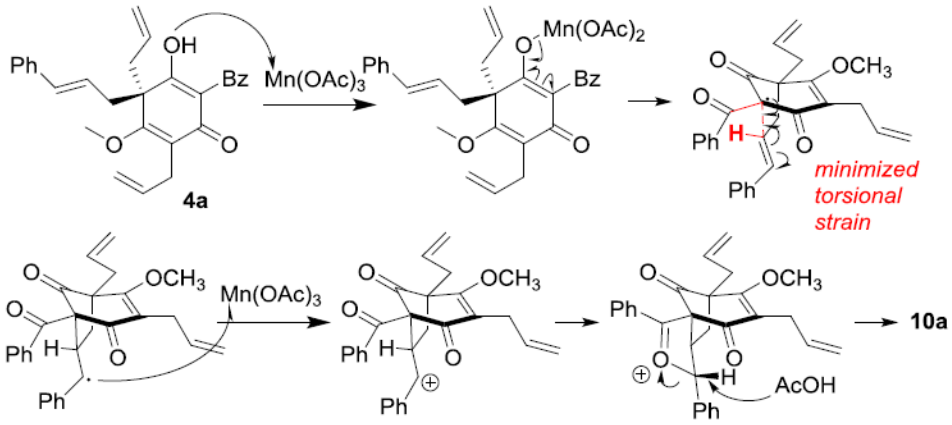
Scheme 1.

Photoisomerization of the styrene moieties of **4a** and isomer **4a′**



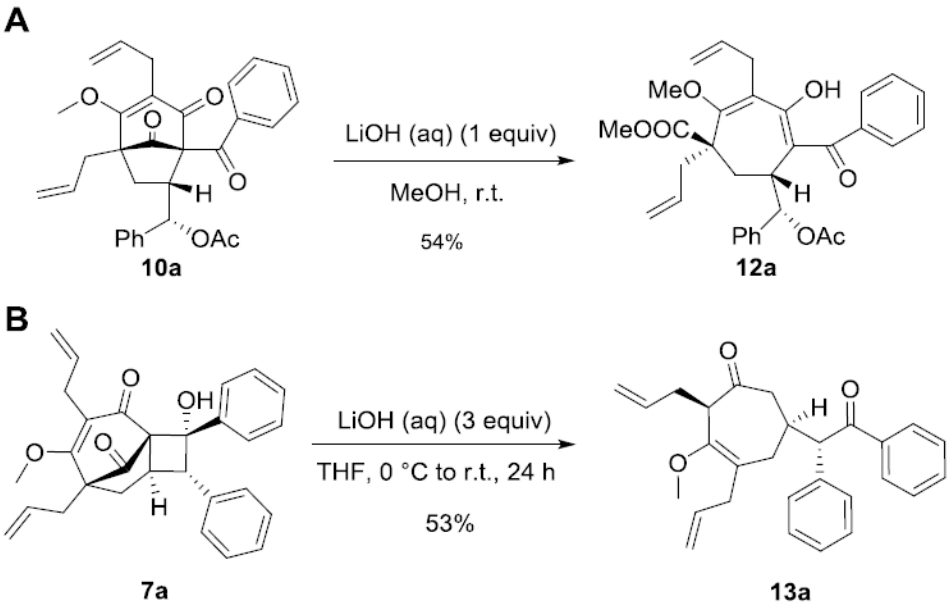
Scheme 2.

Mechanistic proposal for formation of cyclobutanols **7a**/**8a** and [3,2,1]-tricycle **9a**

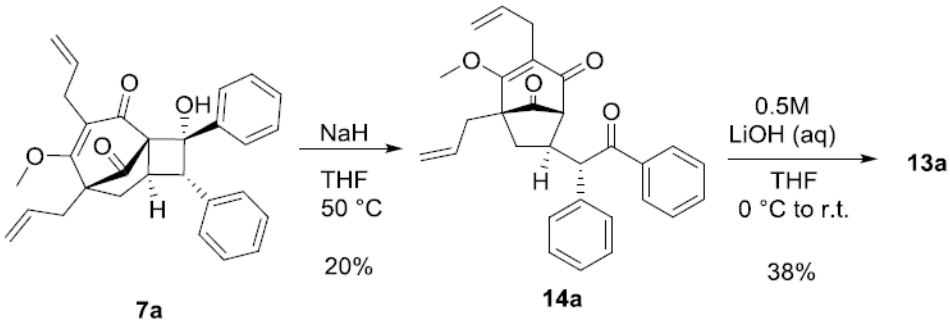


Scheme 3.

Proposed mechanism for formation of [3.2.1]-bicycle **10**



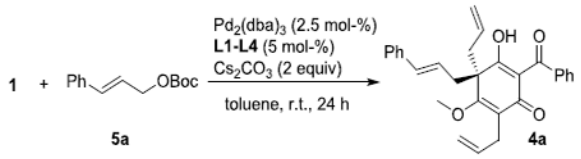
Scheme 4.
Fragmentation of compounds **10a** (A) and **7a** (B)

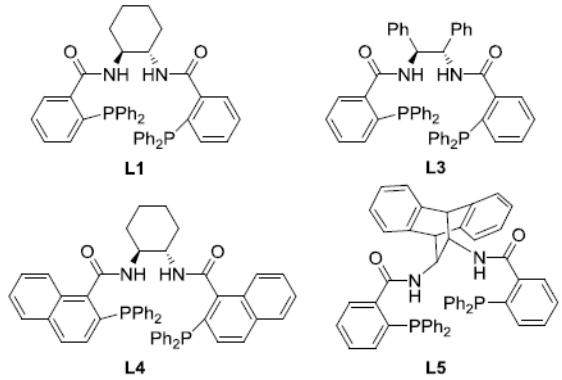


Scheme 5.
Further reactions of scaffold **7a**

Table 1

Asymmetric Cinnamylation: Ligand Screening





Entry	Ligand	Yield[a] [%]	*ee*[b] [%]
1	(*S,S*)-DACH-phenyl Trost (**L1**)	72	99
2	(*R,R*)-DACH-phenyl Trost (**L2**)	81	-97
3	(*S,S*)-DPEDA-phenyl Trost (**L3**)	63	86
4	(*S,S*)-DACH-naphthyl Trost (**L4**)	0	--
5	(*S,S*)-ANDEN-phenyl Trost (**L5**)	44	-24

[a]Yields of isolated products.

[b]Determined by HPLC analysis.

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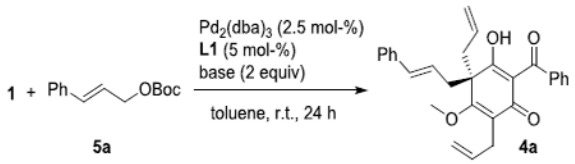
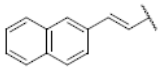
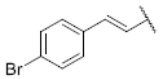
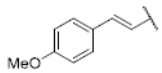
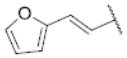
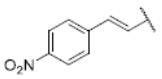
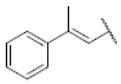
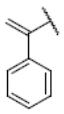
Table 2

Asymmetric Cinnamylation: Substrate Scope



Entry	Substrate	R'	Product	Yield[a] [%]	ee[b] [%]
1	**5b**		**4b**	96	97
2	**5c**		**4c**	87	98
3	**5d**		**4d**	69[c]	91
4	**5e**		**4e**	79[d]	99
5	**5f**		**4f**	77	41
6	**5g**		**4g**	0	-
7	**5h**		**4h**	0	-

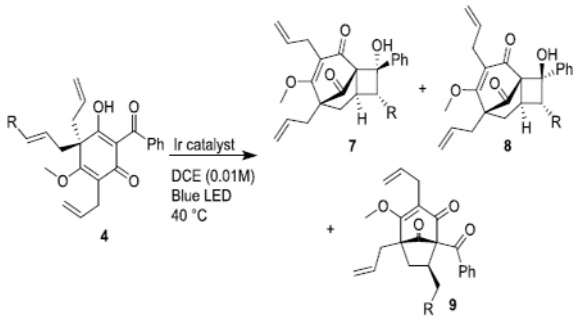
[a]Yields of isolated products.

[b] Determined by chiral HPLC analysis.

[c] 48 h reaction time.

Table 3

Photoreactions of cinnamylated substrates **4**[a]

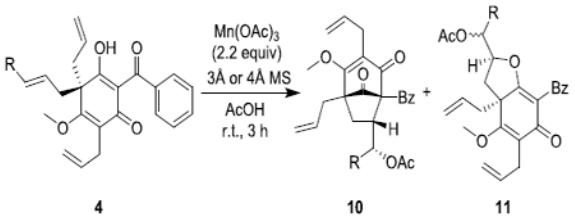


Entry	Substrate	Time [h]	Yield [%] of[a]		
			7	**8**	**9**
1	**4a**	24	22 (**7a**)	13 (**8a**)	11 (**9a**)
2	**4b**	24	20 (**7b**)	-	-
3	**4c**	48	17 (**7c**)	13 (**8c**)	5 (**9c**)
4	**4d**	6	27 (**7d**)	13 (**8d**)	11 (**9d**)
5	**4e**	48	23 (**7e**)	-	-

[a]Yields of isolated products.

Table 4

Oxidative free radical cyclization of cinnamylated substrates **4**[a]



Entry	4	R	Yield of[a]	
			10 [%]	**11 [%]**
1	**4a**	Ph-	19 (**10a**)	-
2	**4c**	4-BrPh-	20 (**10c**)	-
3	**4d**	4-MeOPh-	24 (**10d**)	51 (**11d**, dr = 1:1)

[a]Yields of isolated products.