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Enantioselective Ullmann Ether Couplings: Syntheses of (−)-Myricatomentogenin, (−)-Jugcathanin, (+)-Galeon, and (+)-Pterocarine

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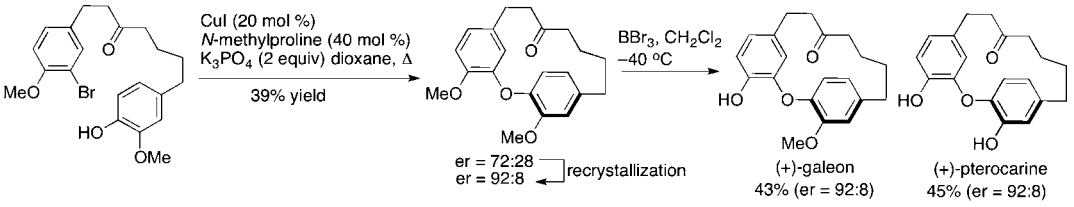
ABSTRACT



The first enantioselective Ullmann cross-coupling reactions to prepare diaryl ethers are reported. The reactions were used to prepare the diarylether heptanoid natural products (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (+)-pterocarine.

The Ullmann ether coupling[1] is a versatile reaction that is used to prepare diarylethers and other types of ethers that cannot be accessed by the Williamson[2] method. Classic Ullmann conditions require high temperatures and stoichiometric copper reagents and often proceed in modest yields. However, modern improvements to this reaction have increased the reactivity as well as chemical yields and lowered reaction temperatures.[3] Such improvements to the Ullmann coupling use ligands to accelerate the reaction and improve the efficiency of the Cu catalyst.[4] Many of the ligands that accelerate the Ullmann reaction happen to be chiral, although, they are often used in racemic form because the product diarylethers are usually achiral.[5]

We hypothesized that use of nonracemic ligands in the presence of Cu salts would render the Ullmann reaction enantioselective, and we decided to evaluate such conditions in the syntheses of the conformationally chiral cyclophane natural products (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (+)-pterocarine (Figure 1). To the best of our knowledge, there are no examples of an enantioselective Ullmann ether synthesis. However, desymmetrization reactions forming C−N bonds were recently reported.[6] Moreover, enantioselective Ullmann couplings could find applications in reagent-controlled syntheses of atropodiasteromeric ether substructures in molecules such as vancomycin.[7] Finally, substituted diarylethers can be chiral depending on their substitution pattern, and an enantioselective Ullmann reaction would find application in the syntheses of such molecules.[8]

Diarylether heptanoids (DAEHs)[9] are a class of natural products isolated from woody plants that are characterized by an oxa[1.7]metaparacyclophane architecture. Members

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(2) Williamson, W. *Liebigs Ann. Chem.* **1851**, *77*, 37–49.
(3) For reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096–3099. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
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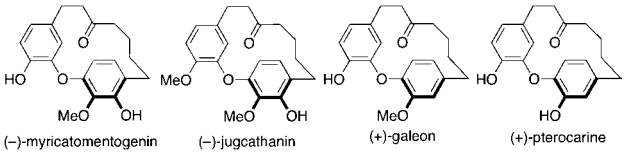
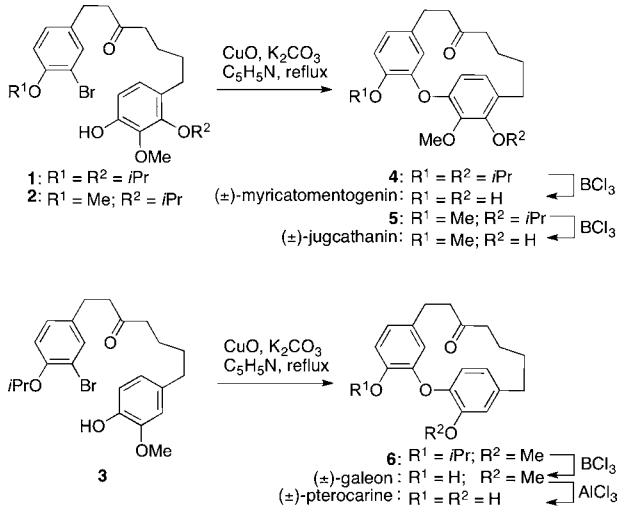


Figure 1. Chiral diarylether heptanoids lacking stereocenters.

Scheme 1. Racemic Synthesis of Chiral Diarylether Heptanoids Lacking Stereocenters



of this natural product family have broad biological activities including leishmanicidal,[10] anti-inflammation,[11] and anticancer activities.[12] The DAEHs have attracted interest from synthetic chemists.[12b,13]

Our interest in the DAEHs arises from their chiral properties.[14] Recently, we showed that of the 16 DAEHs

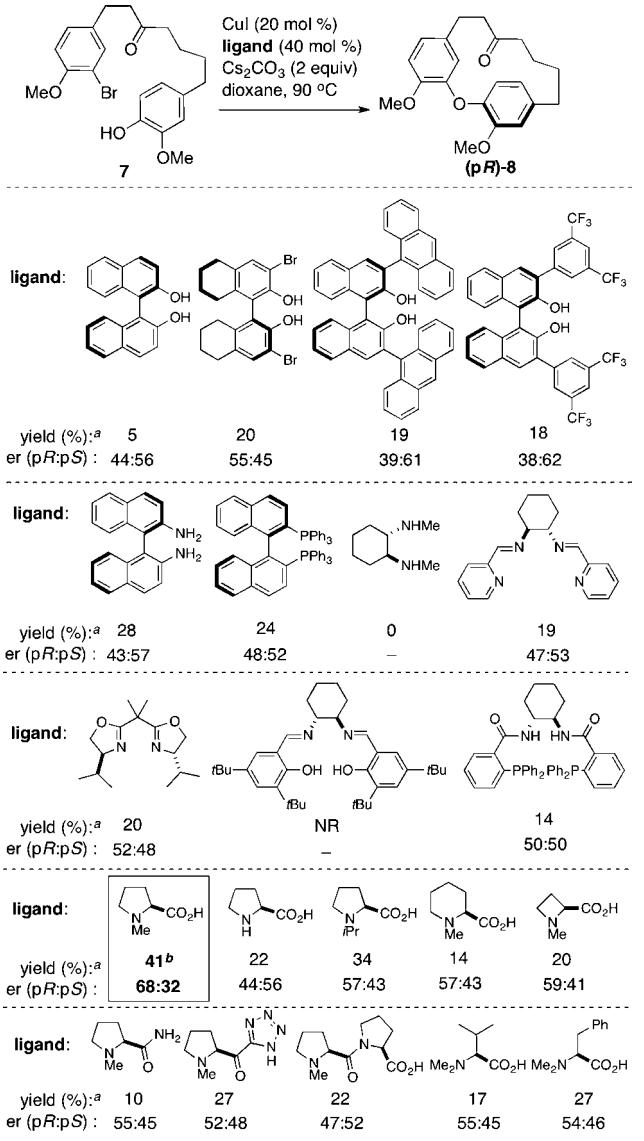


Figure 2. Evaluation of binapthol-type ligands in the Ullmann coupling of **7**. [a]Yield based on recovered starting material. [b] Isolated yield (average of three trials).

that do not possess a stereocenter, 4 DAEHs are chiral: (−)-myricatomentogenin,[15] (−)-jugcathanin,[16] (+)-galeon,[15,17] and (+)-pterocarine.[18] These chiral DAEHs all possess the same *p*R[19] absolute configuration (Figure 1).[14a] Our syntheses of the racemic DAEHs involves an intramolecular Ullmann ether coupling of bromophenols **1**, **2**, and **3** to

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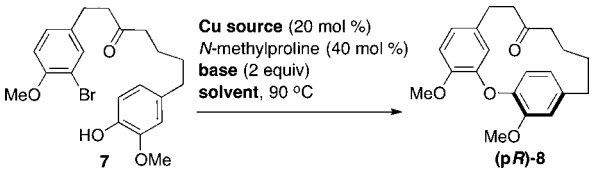
Table 1. Optimization of Reaction Conditions



Cu source	base	solvent	yield (%)[a]	er[b] (pR:pS)
CuI	Cs_2CO_3	MeCN	16	53:47
CuI	Cs_2CO_3	DMF	12	54:46
CuI	Cs_2CO_3	NMP	0	–
CuI	Cs_2CO_3	EtOAc	18	60:40
CuI	Cs_2CO_3	THF	7	61:39
CuI	Cs_2CO_3	TBME	0	–
CuI	Cs_2CO_3	dioxane	41	68:32
$Cu(OTf)_2$	Cs_2CO_3	dioxane	18	57:43
CuBr·DMS	Cs_2CO_3	dioxane	12	58:42
CuTC	Cs_2CO_3	dioxane	5	54:46
$Cu(MeCN)_4BF_4$	Cs_2CO_3	dioxane	13	61:39
Cu(OTf)·PhMe	Cs_2CO_3	dioxane	26	62:38
$Cu(TMEDA)CI_2$	Cs_2CO_3	dioxane	10	58:42
CuI	2,6-lutidine	dioxane	0	–
CuI	DBU	dioxane	0	–
CuI	K_2CO_3	dioxane	18	64:36
CuI	NaOH	dioxane	0	–
CuI	$NaHCO_3$	dioxane	0	–
CuI	**K_3PO_4**	**dioxane**	**39**	**72:28**

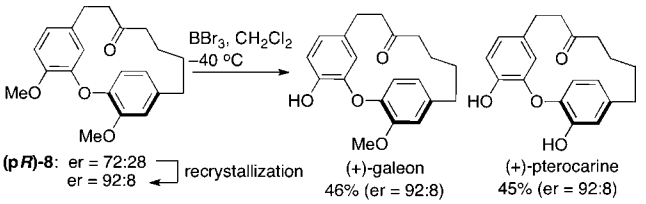
[a] Isolated yield. [b] Determined by HPLC.

give chiral cyclophanes **4**, **5**, and **6**, respectively (Scheme 1). Such reactions convert an achiral starting material to a chiral product, employ a metal catalyst, and are ligand accelerated. These factors suggest the Ullmann ether synthesis could be rendered enantioselective.

Ullmann substrate **7** was prepared using conditions developed in our previous galeon synthesis, and we knew from previous studies that the cyclophane product **8** was a common intermediate for a galeon and pterocarine synthesis (Figure 2).[20] The intramolecular coupling was evaluated using enantiopure ligands known to accelerate the Ullmann reaction and some other privileged ligand structures. Note that racemization of the chiral DAEHs (and alkylated congeners) does not occur at the temperature of the Ullmann cyclization.[14a]

BINOL-type ligands have been used in Cu-catalyzed cross-coupling reactions.[5b,6] We found that use of such ligands in the coupling gave some of the cyclophane product with modest enantioselectivities (Figure 2). Perhaps unsurprisingly, the chemical yields were low, because a significant amount of the phenolic ligand coupled with the bromide functionality of **7**.

Scheme 2. Synthesis of (+)-Galeon and (+)-Pterocarine



Diamines including *N,N*-dimethylcyclohexyldiamine have been used to accelerate Cu-catalyzed cross-coupling reactions.[21] However, use of diamines did not lead to appreciable amounts of the desired product. Similarly, Taillefer has used a chiral Schiff base ligand to increase the rate of the Ullmann reaction.[5a] A moderate yield of the product was observed when Schiff base ligands were used; however, the enantioselectivity was low. Other privelidged ligand classes that have been used in carbon−heteroatom bond formations were evaluated including chiral phosphines,[22] bisoxazolines,[23] salen,[24] and Trost ligands,[25] but yields of the coupling were low and the product was not appreciably enantioenriched.

Gratifyingly, we found that use of *N*-methyl proline in the reaction did lead to increased product yield and encouraging levels of enantioselectivity (Figure 2).[26] Proline and a variety of analogs were then investigated in the reaction. Variation in the *N*-alkyl group, ring size, and the carboxylic acid functionality did not markedly improve the yield or enantioselectivity of the reaction. Use of dipeptides or other *N,N*-dimethyl amino acids did not improve the selectivity.

We then selected *N*-methylproline as the preferred ligand and investigated the other reaction variables (Table 1). Variation of the solvent did not improve the yield or selectivity compared with our standard conditions, nor did variation of the Cu source. Finally, we surveyed a variety of inorganic and organic bases in the Ullmann coupling and found that use of K_3PO_4 gave the product with a higher enantiomeric ratio without a significant decrease in chemical yield.

Dimethyl cyclophane **8** was recrystallized to obtain material that was enantioenriched (92:8 er). It was then converted to a 1:1 mixture of (+)-galeon and (+)-pterocarine without any measurable loss in enantiopurity (Scheme 2).

Diisopropyl-substituted bromophenol **9** was prepared following the same general strategy used for **7**. Cyclization using the optimized conditions gave **10** in moderate yield and enantioselectivity (Scheme 3). Cyclophane **10** could be further purified by recrystallization to give material that was enantioenriched (82:18 er). Treatment of **10** with BCl_3

(20) Unpublished results.

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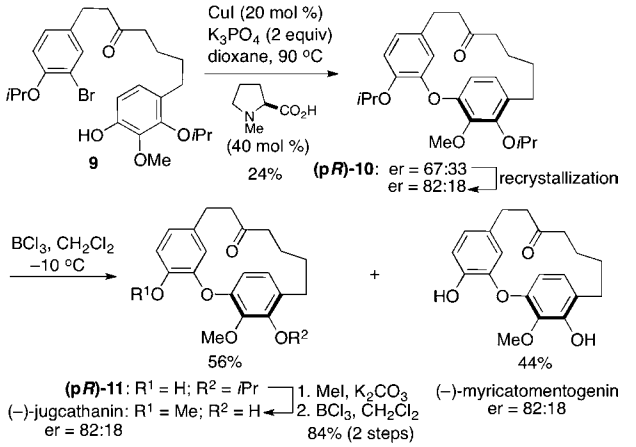
Scheme 3. Synthesis of (−)-Myricatomentogenin and (−)-Jugcathanin



gave a 1:1 mixture of (−)-myricatomentogenin and the product of removal of the more accessible isopropyl ether (**11**) in nearly quantitative yield and no loss in enantioenrichment.[27] Methylation and subsequent deprotection of **11** gave (−)-jugcathanin with no loss in enantiomeric ratio.

In summary, we found that the use of nonracemic ligands render the Ullmann ether synthesis enantioselective. To the best of our knowledge, this is the first example of an enantioselective Ullmann ether coupling. In a survey of a variety of ligands known to accelerate the Ullmann reaction, *N*-methyl proline was the best ligand in terms of chemical yield and enantioselectivity. The nonracemic cyclophane product could be enriched by recrystallization, and the enantioenriched material was used in the first enantioselective synthesis of (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon, and (+)-pterocarine.

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Supporting Information Available. Experimental procedures, spectroscopic data, depiction of ^{1}H and ^{13}C NMR spectra for all new compounds. Chiral HPLC traces for chiral DAEHs. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.