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Synthesis of Phthalans Via Copper-Catalyzed Enantioselective Cyclization/Carboetherification of 2-Vinylbenzyl Alcohols

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Abstract

Enantiomerically enriched phthalans were synthesized efficiently via an enantioselective copper-catalyzed alkene carboetherification reaction. In this reaction, 2-vinylbenzyl alcohols enantioselectively cyclize then couple with vinylarenes. The utility of the method was demonstrated by the enantioselective synthesis of (*R*)-fluspidine, a σ_1 receptor ligand.

Graphical Abstract

Phthalides and phthalans make up the core of important bioactive compounds of both natural and unnatural origins (Figure 1).¹ Their attractive biological profiles have inspired the development of a number of creative approaches toward their de novo synthesis.^{1a, 2}

One surprisingly underexplored direct approach to the synthesis of phthalides and phthalans is the intramolecular cyclization of readily available 2-vinyl benzoic acids and alcohols (Scheme 1).⁴ Along these lines, Kobayashi has reported an iodine-promoted cycloetherification,³ while more recently Waser has reported a palladium-catalyzed carboetherification/cyclization (Scheme 1a) and Zhu has reported a copper-catalyzed carboetherification/cyclization (Scheme 1a).⁴ The synthesis of enantioenriched phthalides from 2-vinyl-benzoic acids has been achieved by Sharpless asymmetric dihydroxylation and subsequent lactonization.⁵ More recently, progress has been made toward enantioselective organo-catalytic bromolactonization and fluorolactonization, reported by Yeung⁶ and

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Author Contributions

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Supporting Information

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Experimental procedures, tabulated characterization data for all new compounds, HPLC traces of chiral products (PDF)

¹H and ¹³C NMR spectra for all new compounds (PDF)

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Rueping,⁷ respectively. A catalytic enantioselective cyclization of benzyl alcohols onto pendant *ortho*- α,β -unsaturated ketones via intramolecular oxa-Michael reactions has also been demonstrated by Ghorai (Scheme 1b).⁸ Herein we disclose a copper-catalyzed enantioselective alkene carboetherification as an approach to the synthesis of enantioenriched phthalans from unactivated 2-vinyl benzyl alcohols (Scheme 1c). Application of the method to the synthesis of (*R*)-fluspidine, a σ_1 receptor ligand, is also demonstrated.

We have disclosed enantioselective copper-catalyzed alkene carboetherifications for the synthesis of chiral tetrahydrofurans.^{9a,b} Related alkene carboetherification methods have also been disclosed by other groups.^{9c-f} We aimed to extend the scope of this powerful methodology to the synthesis of chiral phthalans and phthalides. Using this approach, requisite substrates are 2-vinylbenzyl alcohols and benzoic acids **1**, whose application in metal-catalyzed alkene cyclization/difunctionalization is less common, possibly due to loss of conjugation in the *exo*-cyclization transition state. The envisioned reaction sequence for phthalan formation, analogous to our prior tetrahydrofuran synthesis method,^{9a} is illustrated in Scheme 2. The benzylalcohol **1** is proposed to coordinate to the copper(II) center followed by intramolecular cis-oxycupration. Homolysis of the resulting alkyl-Cu(II) bond provides a methyl radical that can add to vinyl arenes. Oxidation of the resulting benzylic radical then results in formation of the higher substituted vinyl arene **2**.

We investigated the optimal conditions for enantioselective carboetherification of 2-vinylbenzyl alcohols **1a** and **1b** with 1,1-diphenylethylene, as shown in Table 1. Subjecting **1a** to Cu(OTf)₂ (20 mol %), (*S,S*)-*t*-Bu-Box (25 mol %), and 1,1-diphenylethylene (3 equiv) in PhCF₃ at 120 °C in the presence of K₂CO₃ (1 equiv)⁹ provided phthalan **2a** in 90% yield and 97% ee (Table 1, entry 1). An attempt to reduce loading of the Cu(OTf)₂ and (*S,S*)-*t*-Bu-Box to 15 and 18 mol %, respectively, decreased the isolated yield to 74% (Table 1, entry 2). Reducing the reaction temperature to 100 °C resulted in reduced isolated yield (Table 1, entry 3). The reaction of **1a** under optimal conditions (Table 1, entry 1) was performed on 1 mmol scale and resulted in 70% isolated yield of **2a** (>99% ee, Table 1, entry 4). 2-Vinylbenzyl alcohol **1b**, a primary benzyl alcohol, was next investigated. Under the conditions deemed optimal for **1a** (Table 1, entry 1), cycloetherification occurred to provide a 2:2:1 ratio (crude ¹H NMR) of phthalan **2b**, the benzaldehyde derived from **1b**, and benzyl alcohol **1b**, respectively (Table 1, entry 5). The competitive oxidation of the primary benzyl alcohol under these conditions, which employ MnO₂ as the stoichiometric oxidant, was not surprising. Fortunately, upon changing to a milder oxidant, Ag₂CO₃ (200 mol %), 71% of phthalan **2b** could be obtained in 80% ee (Table 1, entry 6). Reducing the amount of Ag₂CO₃ to 100 mol % provided **2b** in even higher yield (93%, Table 1, entry 7). Reducing the reaction temperature to 100 °C resulted in lower conversion (Table 1, entry 8). It should be noted that no reaction was observed when Cu(OTf)₂ was omitted and minimal reaction (ca. 5% conversion) was detected when MnO₂ was omitted in the reaction of **1a** (not shown). Thus, with the optimal conditions in hand (Table 1, entries 1 and 7), the 2-vinylbenzyl alcohol scope was further explored (Scheme 3).

A number of substrate functionalities including Cl, Me, OMe, CF₃, and a tertiary amine were tolerated under the reaction conditions (Scheme 3). Tertiary alcohol substrates

uniformly provided higher levels of enantioselectivity than primary benzyl alcohol substrates (e.g., compare **2a** and **2h** to **2b** and **2c**). A benzoic acid was able to cyclize to give phthalide **2e**, albeit with low enantioselectivity. In this case, the soluble base 2,6-di-*tert*-butyl-4-methylpyridine provided higher conversion than when K₂CO₃ was used, possibly due to the difference in solubility of the intermediate corresponding benzoate salt. (2-(1-Phenylvinyl)phenyl)methanol provided phthalan **2d**, but the enantioselectivity was greatly diminished. The absolute stereochemistry of the products was assigned by conversion of phthalan **2c** to its known corresponding primary alcohol (using OsO₄ and PhI(OAc)₂, then NaBH₄) and optical rotation comparison (see Supporting Information).⁸

A survey of vinylarene coupling partners was also investigated (Scheme 4). While 1,1-disubstituted vinyl arenes are generally the best partners due to their greater ability to react with the presumed carbon radical intermediates, 4-methylstyrene also provided phthalan **2k** in 99% yield and 96% ee. Similarly, reaction with 4-methoxystyrene and unsubstituted styrene (5 equiv) provided 65% and 95% yields of adducts **2l** and **2m** in 99% ee each. The less electron-rich 4-chlorostyrene (5 equiv) underwent the reaction with alcohol **1a** in 55% yield and 99% ee, while the 4-cyanostyrene was unreactive under these conditions. Reaction of **1a** with 2-methoxystyrene provided **2p** in 52% yield and 99% ee, while reaction with 2-bromostyrene provided **2q** in 33% yield and 99% ee. In these reactions with styrenes, use of the soluble 2,6-di-*tert*-butyl-4-methylpyridine instead of K₂CO₃ significantly reduced styrene polymerization. Reaction of **1a** with 1,1-(4-chlorophenyl)ethylene provided phthalan **2r** in 90% yield and 93% ee. Vinyl arenes with exocyclic alkenes provided endocyclic alkenes **2s** and **2t** as major isomers.

The synthetic utility of this enantioselective phthalan synthesis method is illustrated in the enantioselective synthesis of (*R*)-fluspidine, a σ_1 receptor probe (Scheme 5).^{1b-e} This compound was previously obtained in enantioenriched form via chiral HPLC resolution,^{1c} and more recently by enantioselective synthesis using a catalytic asymmetric reduction as the key step.^{1e} Our synthesis began with commercially available 2-bromostyrene, which was subjected to lithium-halogen exchange followed by treatment with *N*-benzoyl-piperidine-4-one, providing the corresponding 2-vinylbenzyl alcohol in 78% yield. Enantioselective carboetherification with 1,1-diphenylethylene provided chiral phthalan **2u** in 81% yield and 86% ee. Alternatively, reaction with 4-methylstyrene provided adduct **2v** in 87% yield and 89% ee. Oxidative cleavage of the alkene followed by reduction of the resulting aldehyde and concomitant reduction of its amide provided the known primary alcohol **4**.^{1c,e} Application of **2v** instead of **2u** in this synthesis is slightly more atom economical (less carbons removed in oxidation step). Direct fluorination of **4** with DAST as previously reported^{1e} provided (*R*)-fluspidine. The optical rotation of (*R*)-fluspidine (**5**) was similar to the reported value (Scheme 5).^{1c,e} Our enantioselective synthesis fluspidine is two steps shorter than the racemic synthesis^{1c} and five steps shorter than the previously reported enantioselective synthesis.^{1e}

In summary, copper-catalyzed alkene carboetherification is an effective method for the synthesis of enantioenriched phthalans from 2-vinyl benzylalcohols. Further demonstrations of the scope of the copper-catalyzed enantioselective alkene carboetherification are underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bioactive phthalides and phthalans.

Related literature examples:

This work:

Scheme 1.

Phthalides and Phthalans from 2-Vinylbenzyl Alcohols and 2-Vinylbenzoic Acids

Scheme 2.
Proposed Copper-Catalyzed Carboetherification Mechanism

Scheme 3. Scope with Respect to 2-Vinylbenzyl Alcohol or 2-Vinylbenzoic Acid^a

Scheme 4.

Scope of the Alkene Coupling Partner^a

Scheme 5.
Enantioselective Synthesis of (*R*)-Fluspidine

Table 1.

Reaction Optimization ^a

<p>1a, R = Me 1b, R = H</p> <p>2a 2b</p>				
entry	substrate	oxidant (mol %) ^b	yield (%) ^c	ee (%) ^d
1	1a	MnO ₂ (260)	90	97
2 ^e	1a	MnO ₂ (260)	74	98
3 ^f	1a	MnO ₂ (260)	78	
4 ^g	1a	MnO ₂ (260)	70	>99
5 ^h	1b	MnO ₂ (260)	ca. 40	
6	1b	Ag ₂ CO ₃ (200)	71	80
7	1b	Ag ₂ CO ₃ (100)	93	81
8 ^{f,h}	1b	Ag ₂ CO ₃ (100)	ca. 56	

^aReaction conditions: Cu(OTf)₂ (0.037 mmol, 20 mol %) and (*S,S*)-*t*-Bu-Box (25 mol %) were complexed in PhCF₃ (1 mL) at 60 °C. After 2 h, oxidant, alcohol **1** (0.185 mmol) in PhCF₃ (1 mL), K₂CO₃ (1 equiv), 1,1-diphenylethylene (3 equiv), and 4 Å mol. sieves were added at rt and the mixture was heated and stirred for 24 h at 120 °C in a sealed tube.

^bMnO₂ (85%, <5 μ was used).

^cIsolated yield unless otherwise noted.

^dEnantioselectivity determined by chiral HPLC.

^eReaction run with 15 mol % Cu(OTf)₂ and 18 mol % (*S,S*)-*t*-Bu-Box.

^fReaction run at 100 °C.

^gThis reaction used substrate **1a** at 1 mmol scale.

^hYield estimated by crude ¹H NMR. Ca. 40% of the benzaldehyde derived from **1b** was also formed.