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Stereocontrolled Synthesis of Contiguous C(sp^3)−C(aryl) Bonds by Lanthanide(III)-Catalyzed Domino Aryl-Claisen [3,3]-Sigmatropic Rearrangements

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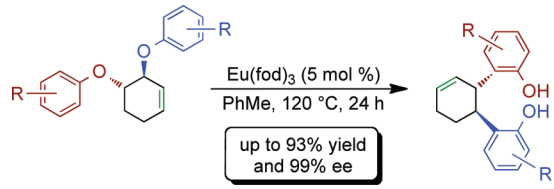
ABSTRACT



A domino [3,3]-sigmatropic aryl-Claisen rearrangement of cyclic and acyclic bisaryloxy-substituted alkenes can be performed in high yield by using Ln(fod)$_3$ catalysis to obtain bisphenolic products incorporating two contiguous aryl−C(sp^3) bonds. Stereospecific rearrangement was observed for cyclic substrates. The precursor diaryl ethers were typically synthesized from the corresponding diols by double arylation procedures using either copper catalyzed coupling of aryltrifluoroborate salts or by S$_N$Ar reaction.

Domino transformations constitute an effective strategy for natural product and complex molecule synthesis by achieving multiple asynchronous reactions using one-pot protocols.[1] Sequences that feature sigmatropic rearrangements, such as the Cope or Claisen reaction, are especially powerful since they can be used to efficiently alter C−C connectivity in a regio- and stereocontrolled manner.[2] Examples include para-Claisen/Cope reactions,[3] the oxy-Cope/Claisen/ene reaction,[4] the double Ireland−Claisen reaction,[5] the [2,3]/*o*-aryl-Claisen reaction of aryl propargyl sulfoxides and aryl propargylamine oxides,[6] and the double aryl-Claisen rearrangement.[7] The latter example was developed by Hiratani and co-workers for the formation of two noncontiguous aryl−CH$_2$R bonds in a nonasymmetric transformation, and was used for the synthesis of rotaxane supramolecular assemblies.

The occurrence of contiguous aryl−C(sp^3) motifs is evident in recently isolated or biologically relevant natural products.[8] Although there are methods for the synthesis of such motifs, there are no general methods for the direct stereoselective formation of two or more contiguous aryl−C(sp^3) bonds (i.e., for which aryl−C bond formation occurs).[9,10] Our recent interest in the development of stereocontrolled [3,3]-sigmatropic rearrangements[11] has led

(1) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, Germany, 2006.
(2) (a) *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007. (b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2010**, *38*, 3133–3148. (c) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (d) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–247. (f) Paquette, L. A. *Tetrahedron* **1997**, *41*, 13971–14020.
(3) Al-Maharik, N.; Botting, N. P. *Tetrahedron* **2003**, *59*, 4177–4181.
(4) Sauer, E. L. O.; Barriault, L. *Org. Lett.* **2004**, *6*, 3329–3332.
(5) (a) Curran, D. P.; Suh, Y. G. *J. Am. Chem. Soc.* **1984**, *106*, 5002–5004. (b) Curran, D. P.; Suh, Y. G. *Tetrahedron Lett.* **1984**, *25*, 4179–4182. (c) Curran, D. P.; Suh, Y. G. *Carbohydr. Res.* **1987**, *171*, 161–191.
(6) Majumdar, K. C. *Synlett* **2008**, *16*, 2400–2411.
(7) Hiratani, K.; Albrecht, M. *Chem. Soc. Rev.* **2008**, *37*, 2413–2421.

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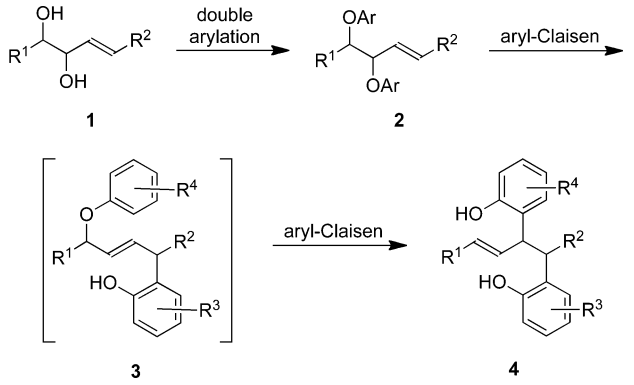
us to addressing the challenge of developing a versatile, mild, and general method for the formation of such structural motifs in an enantio- and diastereoselective fashion. Herein, we report a new lanthanide-catalyzed domino aryl-Claisen reaction as an effective and general means to stereoselectively access bisphenols with contiguous aryl−C(sp^3) bonds.

It was envisaged that the synthesis of bisarylated targets such as **4** could be accessed via a domino aryl-Claisen rearrangement approach from an appropriately functionalized 1,2-dioxygenated precursor such as diol **1** (Scheme 1). These

Scheme 1. General Synthetic Route to Bisphenol **4**



1,2-diols (either acyclic or cyclic) that are adjacent to alkenyl π-bonds would in turn be accessible through standard stereoselective methods such as alkene dihydroxylation. A stepwise or unprecedented concomitant dual arylation of **1** would then be required to form bisaryl ether domino aryl-Claisen precursor **2**. The key domino aryl-Claisen rearrangement would proceed via the intermediacy of **3** to give product **4**. The rearrangement of the second aryl ring can *only* occur following the allylic transposition that happens as a result of the initial aryl-Claisen rearrangement of **2** into **3**, a defining feature of a domino reaction. The stereochemistry of the newly formed aryl−C(sp^3) bonds would be controlled by the diol and alkene stereochemistry in **1**. Thus, as a result of suprafacial migration, the stereochemistry of **2** should define the stereoconfiguration of the product. The overall transformation of **2** into **4** would achieve the one-pot synthesis of two contiguous aryl−C(sp^3) bonds.

The rearrangement of **2a** into **4a** was chosen for proof of concept studies. The effective O-arylation of secondary alcohols is still a difficult process. The only synthetic method that encompasses both a wide substrate scope and arene variability are copper(II)-catalyzed routes.[12] Hence, a modifed mild Cu(II)-catalyzed aryl ether synthesis[13] using potassium aryltrifluoroborate salts was employed on *trans*-cyclohex-3-ene-1,2-diol[14] for the formation of **2a**.[15] For substrates incorporating electron deficient arenes a one-pot double S_NAr was performed using conditions based upon an existing monoarylative S_NAr procedure.[16] Both routes achieve an unprecedented double arylation of sterically hindered secondary vicinal hydroxyls to give bisaryl ethers in modest yields ranging from 14% to 68%.

Various methods to effect the domino aryl-Claisen rearrangement on **2a** to form **4a** were attempted. Use of classical thermal conditions on **2a** using H_2O at 160 °C for 3 d did not produce **4a**. However, microwave-assisted aryl-Claisen rearrangement[17] of **2a** in DMF at 250 °C for 1 h afforded 56% of **4a**, although several byproducts were formed under these harsh conditions. The use of europium(III)-tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate) (Eu(fod)$_3$) to effect a high-yielding aryl-Claisen rearrangement with very good chirality transfer has been previously reported,[9a,18,19] whereas stronger Lewis acidic lanthanide triflates led to racemization.[18] Application of the domino rearrangement on **2a** using 5 mol % Eu(fod)$_3$ in tetrachloroethane at 120 °C for 6 h[20] afforded **4a** in 60% yield (Table 1). Further screening indicated the mildest conditions that resulted in the highest yield of **4a**, and using the most environmentally benign solvent was Eu(fod)$_3$ in PhMe at 120

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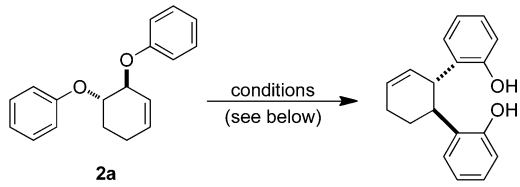
(20) Reaction conditions were modified from ref 19c.

Table 1. Domino Aryl-Claisen Rearrangement Optimization



2a 4a

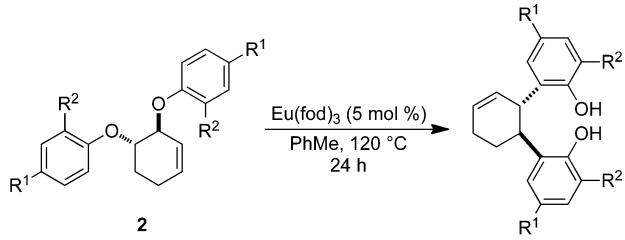
entry	catalyst[a]	solvent	temp (°C)	time (h)	yield (%)[b]
1	none	$C_2H_2Cl_4$	160	24	24
2	Eu(fod)$_3$	$C_2H_2Cl_4$	120	6	60
3	Eu(fod)$_3$	$C_2H_2Cl_4$	160	6	92
4	Er(fod)$_3$	$C_2H_2Cl_4$	160	6	88
5	Yb(fod)$_3$	$C_2H_2Cl_4$	160	6	92
6	Pr(fod)$_3$	$C_2H_2Cl_4$	160	6	84
7	Eu(fod)$_3$	PhCl	120	24	92
8	Eu(fod)$_3$	PhMe	120	24	92

[a] 5 mol % loading. [b] After column chromatography.

°C for 24 h.[21] Under these reaction conditions **4a** was afforded in high yield (92%). The corresponding monorearranged product was not observed. The relatively low temperature used in the reaction supports the notion that Eu(III) catalyzes both sigmatropic rearrangement steps of the domino cascade.

A study on substituent effects and the stereospecificity of the domino aryl-Claisen were subsequently performed (Table 2).

Table 2. Cyclic Substrate Scope for the Domino Aryl-Claisen Rearrangement



2 4

substrate	R^1	R^2	chirality	yield (%)[a]
2a	H	H	*rac*	92
2b	SMe	H	*rac*	94
2c	OMe	H	*rac*	96
2d	F	H	*rac*	96
2e	NO_2	H	*rac*	10
2f	H	NO_2	*rac*	27[b]
2g	OMe	H	(1*S*,2*S*)	93 (≥99% ee)
2h	F	H	(1*S*,2*S*)	97 (≥99% ee)

[a] After column chromatography. Enantiomeric excess determined by chiral HPLC. [b] 15 mol % Eu(fod)$_3$ used instead.

Mesomeric electron donating groups on the aryl rings resulted in slightly increased yields of **4**, whereas an *o*- or *p*-nitro group resulted in lower yields. Presumably as the Lewis basicity of the ethereal oxygens of **2** decreases, the efficacy of Eu(III) catalysis is diminished. For **2f**, some decomposition through ionization of the substrate and/or intermediate also contributes to lower product yields. Domino aryl-Claisen rearrangement of enantiopure **2g** and **2h** (synthesized by Cu(II)-catalyzed dual arylation of enantiopure cyclohex-3-ene-1,2-diol) occurs stereospecifically.

The cyclohexenyl π-bond in **4a** could be reduced under catalytic hydrogenation conditions with H_2 (1 atm) and 10% Pd/C (10 mol %) in 94% yield to form the intriguing C_2-symmetric bisphenol **5a** (eq 1). For domino aryl-Claisen product validation, the X-ray crystal structure of **4f** and **5a** was solved (Figure 1).[22]

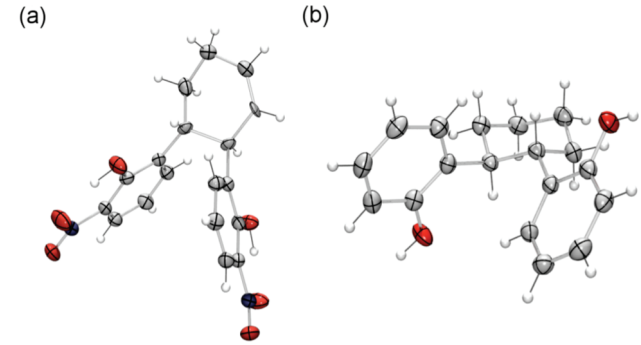
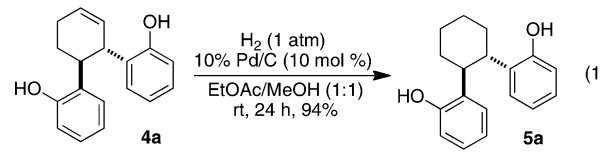


Figure 1. ORTEP X-ray crystal structure display of (a) **4f** and (b) **5a** both with thermal ellipsoids at 50% probability.



4a 5a

The domino aryl-Claisen rearrangement can also be applied on acyclic substrates. Substrate synthesis using Cu(II)-catalyzed double arylation with $ArBF_3K$ salts of a *syn*-1,2-diol was unsuccessful due to cyclic boronic ester formation, and a double Mitsunobu reaction was also ineffective. However, a route using Pd(0)-catalyzed vinyloxirane ring-opening proved to be successful (Scheme 2). Monoarylated precursor **7** was synthesized as a mixture of diastereomers (92:8 *syn*:*anti*) from **6** in 67% yield, through the Pd(0)-catalyzed opening of α,β-unsaturated γ,δ-epoxy esters under double inversion with $B(OPh)_3$.[23] Cu(II)-

(21) A reviewer suggested performing this reaction in a microwave. However, PhMe is a poor solvent for microwave reactions. In ref 9a, microwave conditions were used for a mono-rearrangement, yet PhCl and 30−120 mol % Eu(fod)$_3$ were required. We consider the use of much lower catalyst loadings and the use of a more environmentally benign solvent to be a preferable protocol.

(22) CCDC 716574 and 716575 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

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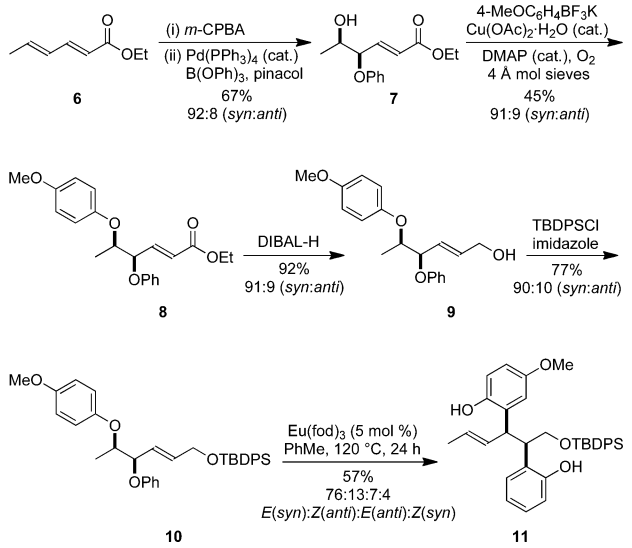
Scheme 2. Synthesis and Rearrangement of Linear Substrate **10**



catalyzed monoarylation to form **8**, DIBAL-H reduction to formallylic alcohol **9**, and TBDPS protection yielded **10** as a 90:10 *syn*:*anti* mixture of diastereomers. TBDPS protection was performed to prevent the primary hydroxyl from interacting with the catalyst due to the oxophilicity of Eu(III). The domino aryl-Claisen rearrangement of **10** formed an inseparable 76:13:7:4 *E*(*syn*):*Z*(*anti*):*E*(*anti*):*Z*(*syn*) mixture of **11** in 57% yield. The formation of this mixture can be rationalized in terms of a reaction manifold in which *E*/*Z*-scrambling occurs during both sigmatropic rearrangement steps of the domino process (Scheme 2).[18,24]

The stereospecific formation of bisphenols with two contiguous aryl−C(sp^3) centers has been achieved through the rearrangement of bisaryl ethers via the lanthanide(III)-catalyzed domino aryl-Claisen reaction. Rearrangements occur with high stereoselectivity for cyclic substrates, but with lower diastereoselectivity for an acyclic substrate. Futher synthetic studies including in-depth investigations of substrate scope, mechanistic studies, and applications of domino aryl-Claisen rearrangements and other related transformations will be reported in due course.

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Supporting Information Available: Procedures, characterization, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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