Communication

Synthesis of Dihydronaphthalenes via Aryne Diels–Alder Reactions: Scope and Diastereoselectivity

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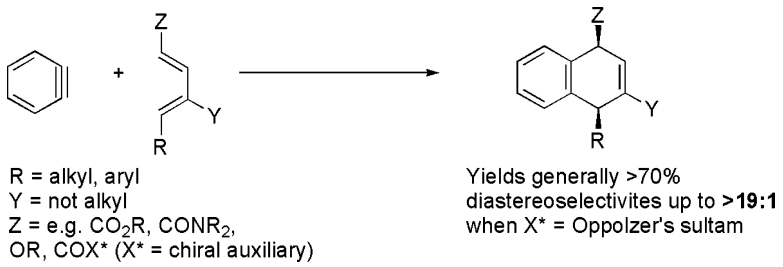

R = alkyl, aryl
Y = not alkyl
Z = e.g. CO_2R, $CONR_2$, OR, COX* (X* = chiral auxiliary)

Yields generally >70%
diastereoselectivites up to **>19:1**
when X* = Oppolzer's sultam

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Synthesis of Dihydronaphthalenes via Aryne Diels−Alder Reactions: Scope and Diastereoselectivity

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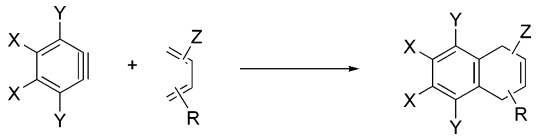
We have been developing approaches to hydronaphthalenes using various stereo- and enantioselective ring-opening procedures. A number of useful transformations have emerged but most are best suited to preparing 1,2-substituted analogues.[1] The need for methods that directly form 1,4-substitution patterns is related to the diverse biological activity observed with this "privileged" structural class. Some methods are known,[2−4] but simpler approaches are of interest. A very attractive strategy is the Diels−Alder reaction between an aryne (dehydrobenzene)[5] and an acyclic diene (Scheme 1), but the

Scheme 1. Aryne Diels−Alder Reaction with Acyclic Dienes

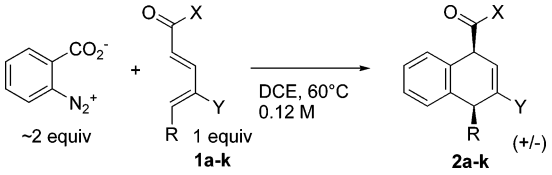


scope and utility of this approach have not been investigated in depth since the first report by Wittig in the 1960s.[6] Aryne Diels−Alder (ADA) reactions with cyclic dienes are frequently utilized; however, reactions with functionalized acyclic dienes are much less common.[7] A method leading to substituted 1,4-dihydronaphthalenes would be highly desirable, especially if at least one of the substituents could be a heteroatom or an easily manipulated functional group. We now report a direct and stereoselective route to *cis*-substituted dihydronaphthalenes via ADA reactions with acyclic dienes and demonstrate the utility of the products with a short synthesis of sertraline.

We began our study by reacting various acyclic 1,3-dienes with benzyne generated from benzenediazonium-2-carboxylate (BDC) using Friedman's procedure.[8] Ethyl sorbate **1a** (1.2 equiv) and BDC in 1,2-dichloroethane (DCE) at 60 °C gave the desired cycloadduct **2a** cleanly by NMR (crude yield 60%). However, **2a** and the excess ethyl sorbate were inseparable by TLC and column chromatography. We repeated the reaction using ethyl sorbate as the limiting reagent with a slurry of an excess (∼2 equiv) of BDC in DCE at 60 °C to provide **2a** in 74% yield.[9−11] Several other benzyne generation methods were also investigated, all of which gave inferior results.[9]

We prepared a collection of functionalized dienes[9] for screening in the Diels−Alder reaction with benzyne (Table 1). Carbonyl-substituted dienes were used since these are easy to synthesize via Horner−Emmons−Wadsworth reactions. We observed that the cycloaddition yields were consistently good, which is noteworthy considering that reactions of *cyclic* dienes under similar conditions with benzyne usually gave yields <70%. Dienyl esters and amides (**1h**) gave clean reactions; however, dienyl acid **1e** gave a complex mixture, perhaps due to insertion into the O−H bond.[5] Aryl substituents with both electron-withdrawing and electron-donating groups are tolerated (**1c**−**f**), except that the strongly electron-donating dimethylamino group gave no trace of cycloadduct (**1g**). The reaction can also proceed with some trisubstituted dienes. An electron-withdrawing ester group in the 3-position gave quantitative

Table 1. Cycloadditions with Carbonyl-Substituted Dienes[a]



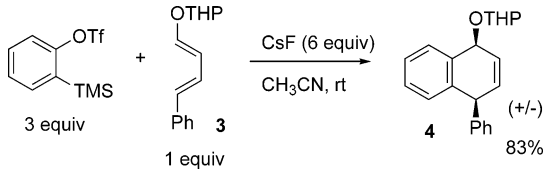
diene	R	X	Y	product	yield[b] (%)
1a	Me	OEt	H	**2a**	74
1b	Ph	OEt	H	**2b**	84
1c	3,4-ClPh	OEt	H	**2c**	86
1d	3,4-ClPh	OBn	H	**2d**	78
1e	3,4-ClPh	OH	H	**2e**	(50)[c]
1f	4-(MeO)Ph	OEt	H	**2f**	75
1g	4-(Me_2N)Ph	OEt	H	**2g**	(0)[d]
1h	Ph	N(*i*-Pr)$_2$	H	**2h**	54
1i	Ph	OMe	Me	**2i**	(0)[e]
1j	Ph	OEt	Br	**2j**	80
1k	Ph	OMe	CO_2Et	**2k**	85[f]

[a] All reactions were performed according to the optimized conditions detailed in the Supporting Information. [b] Isolated yield (NMR yield with acetone or dichloromethane as standard is in parentheses). Unless otherwise noted, all diene starting material was consumed. [c] Complex mixture. [d] No reaction. [e] No reaction, but diene was consumed. [f] Isomerization of the product occurred with flash chromatography.

yields by NMR (**1k**), though the product was unstable to column chromatography with silica gel. A diene with a methyl group in the 3-position (**1i**) was consumed in the reaction but gave no desired product by NMR.[12] The best result was obtained with a bromo group (**1j**), which gave the product in 80% isolated yield. The expected *cis* stereochemistry from a concerted [4+2] process was confirmed by an X-ray structure of product **2h**.[9]

Cycloadditions with NC-, NO_2-, and O-substituted dienes are also possible.[9] Particularly with O-substituted diene **3**, the ADA reaction proceeds efficiently under the standard conditions with BDC to generate **4** in 77% yield,[13] or alternatively with benzyne generated from 2-(trimethylsilyl)phenyl triflate and CsF in CH_3-CN (Scheme 2).[14]

Scheme 2. Cycloaddition with Heterosubstituted Diene



We have also adapted the ADA reaction to the preparation of enantiomerically enriched products. Our first approach was to attach a chiral auxiliary to a diene carbonyl group. Poor to moderate diastereoselectivities (1:1 to 3.5:1) were obtained using several different auxiliaries under our standard conditions with BDC. However, excellent diastereoselectivities (>19:1) are obtained with

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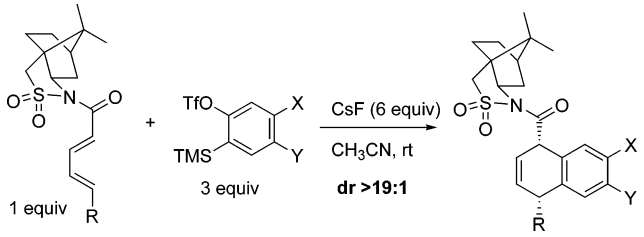
Table 2. Highly Diastereoselective Aryne Cycloadditions

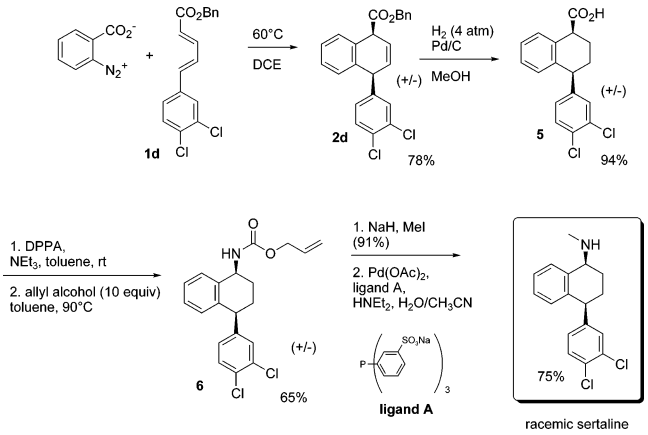


diene	R	X	Y	product	yield (%)
1l	Me	H	H	**2l**	60
1m	Ph	H	H	**2m**	48
1n	3,4-ClPh	H	H	**2n**	40
1o	3,4,5-(MeO)Ph	H	H	**2o**	45
1l	Me	−OCH_2O−		**2p**	51

Oppolzer's sultam, specifically when using benzyne generated from 2-(trimethylsilyl)phenyl triflate and CsF in CH_3CN (Table 2). The assignment of the diastereomers **2l** and **2m** is based upon ROESY NMR measurements. In addition, this method was successfully extended to cycloadditions with substituted arynes (**2p**, Table 2).

To demonstrate the utility of the alkoxycarbonyl-substituted 1,4-dihydronaphthalenes as precursors to medicinally important products, a Curtius rearrangement was utilized as a key step in a synthesis of racemic sertraline[15] (Scheme 3). Moreover, **2n**, which

Scheme 3. Synthesis of Sertraline



is obtained almost diastereomerically pure in 40% (unoptimized) yield, is a precursor for the corresponding asymmetric synthesis.

The Diels−Alder reaction between benzyne and dienyl ester **1d** proceeded in good yield using the standard protocol. Cycloadduct **2d** was hydrogenated and deprotected in one pot without epimerization or loss of the aryl chlorides to give acid **5**. The benzyl ester was essential, since the analogous ethyl ester could not be hydrolyzed under basic conditions (KOH, THF/water, 60 °C; K_2CO_3, MeOH/water, room temperature) without epimerization of the sensitive benzylic center alpha to the carbonyl group.

The Curtius rearrangement of **5** was best conducted by formation of the acyl azide (DPPA or $ClCO_2Et$ followed by NaN_3) and then slow addition to a hot solution (90 °C) of allyl alcohol in toluene. Allyl carbamate **6** was isolated in 65% yield and subsequently N-methylated and deprotected with a water-soluble Pd(0) catalyst[16] to give sertraline, with NMR spectrum consistent with that reported by workers at Pfizer.[17]

In conclusion, we have reported that the aryne Diels−Alder reaction with acyclic dienes is a useful method for the synthesis of functionalized 1,4-dihydronaphthalenes. Reactions with electron-withdrawing substituents on the diene generally proceed favorably, indicating that an inverse electron-demand Diels−Alder pathway might be operating in these cases. The first diastereoselective aryne Diels−Alder reaction to provide enantiomerically enriched cycloadducts was developed.

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Supporting Information Available: Experimental procedures, additional data tables, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) This substrate may be prone to, e.g., an ene reaction, which could lead to a complex mixture of products. See for example ref 6.
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