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Enantioselective (Formal) Aza-Diels−Alder Reactions with Non-Danishefsky-Type Dienes

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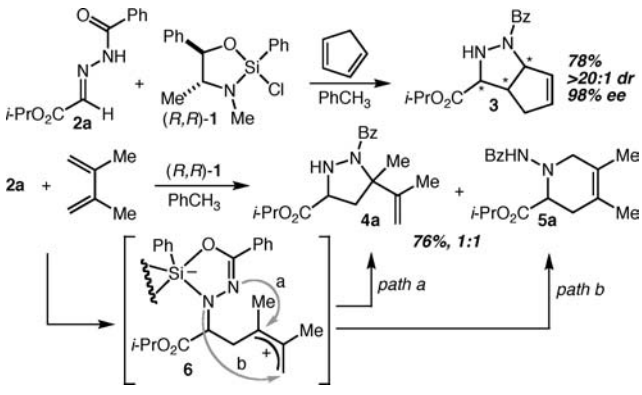
Abstract: Enantioselective (formal) aza-Diels−Alder reactions between acylhydrazones and non-Danishefsky-type dienes have been developed. The reactions are promoted by a simple and economical chiral silicon Lewis acid and are typically conducted at ambient temperature. Both glyoxylate- and aliphatic aldehyde-derived hydrazones may be employed, as may variously substituted dienes, leading to the synthesis of a diverse array of tetrahydropyridines with good to excellent levels of enantioselectivity.

On any list of important heterocycles, both for natural products chemistry and medicinal chemistry, piperidines would figure most prominently. While countless methods may be imagined for the synthesis of such structures, the diene−imine [4 + 2] cycloaddition (aza-Diels−Alder, ADA) reaction must surely rank as one of the more direct and potentially versatile methods.[1] Despite this, it is only recently that the first examples of enantioselective variants of this reaction have been developed.[2] However, the highly enantioselective reactions that have been reported are mostly limited to the use of Danishefsky-type dienes, significantly limiting the scope of the reaction. We describe here the development of enantioselective (formal) ADA reactions with non-Danishefsky-type dienes employing a simple and practical silane Lewis acid.

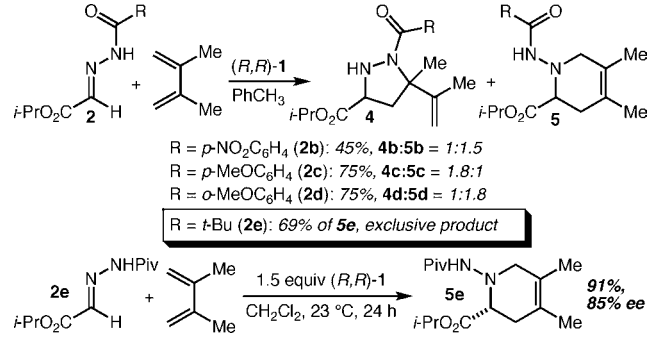
We have previously reported the use of silane **1**[3] with acylhydrazones in [3 + 2] cycloaddition reactions with electron-rich alkenes.[4] Attempts to divert the reaction course to a [4 + 2] pathway focused first on cyclopentadiene, but when the complex formed from the reaction of hydrazone **2a** with silane **1** was treated with cyclopentadiene, pyrazolidine **3** was the exclusive product (Scheme 1). However, when 2,3-dimethyl-1,3-butadiene was employed, a 1:1 mixture of [3 + 2] product **4a** and [4 + 2] product **5a** was obtained in 76% yield. We have established that the [3 + 2] cycloaddition reaction proceeds in a stepwise fashion,[4] and these results may be rationalized using this framework. Thus, initial attack of the diene on the silane−hydrazone complex results in allyl cation intermediate **6**, which can collapse to give the [3 + 2] product **4a** (path a) or the [4 + 2] product **5a** (path b).

Scheme 1



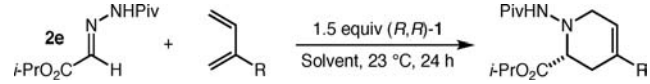
Electronic tuning of the hydrazone aryl group was pursued as a means of perturbing the ratio of products. Thus, whereas electron-poor hydrazone **2b** gave a 1:1.5 ratio of products **4b** and **5b**, electron-rich hydrazone **2c** led to a 1.8:1 ratio of products **4c** and **5c** (Scheme 2). Interestingly, however, *o*-methoxybenzoylhydrazone **2d** favored the production of the [4 + 2] product **5d** (1:1.8), suggesting that steric factors might play an important role as well. This led to an examination of pivaloyl hydrazone **2e**, which produced **5e** as the exclusive product in 69% yield. It was subsequently found that the reaction was best conducted at room temperature in CH_2Cl_2 with 1.5 equiv of silane **1**. Under these conditions, **5e** was isolated in 91% yield and 85% ee.

Scheme 2



A brief survey of the scope of the reaction with respect to the diene structure was carried out (Table 1). Isoprene and other 2-alkyl-1,3-butadienes uniformly provide the products in near-quantitative yields and with good levels of enantioselectivity (entries 1−3). The phenyl-substituted diene gives a lower ee (entry 4), but this can be reversed by using toluene as the solvent (entry 5). In contrast, the *p*-BrC_6H_4-substituted diene performs as well as the alkyl-substituted dienes (entry 6). Finally, we have demonstrated a 3.8 mmol (of **2e**) scale preparative reaction with this diene using reduced (1.3 equiv) silane loadings (entry 7). The product was isolated by recrystallization in 70% yield and 98% ee, and the pseudoephedrine was recovered in 93% yield.

Table 1. Enantioselective Diene−Acylhydrazone [4 + 2] Reactions



entry	R	solvent	yield (%)	ee (%)
1	Me	$CHCl_3$	96	85
2	$PhCH_2CH_2$	$CHCl_3$	99	87
3	$PMBOCH_2CH_2$	$CHCl_3$	95	90
4[a]	Ph	$CHCl_3$	99	−81
5	Ph	$PhCH_3$	66	95
6[a]	*p*-BrC_6H_4	$CHCl_3$	99	−86
7[b]	*p*-BrC_6H_4	$CHCl_3$	70	98

[a] The enantiomeric silane Lewis acid (*S*,*S*)-**1** was used in this reaction. [b] Conditions: 3.8 mmol of **2e**, 1.3 equiv of (*R*,*R*)-**1**, and 2.0 equiv of diene. (*R*,*R*)-Pseudoephedrine was recovered in 93% yield.

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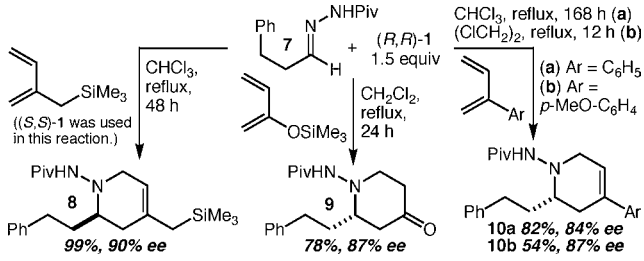
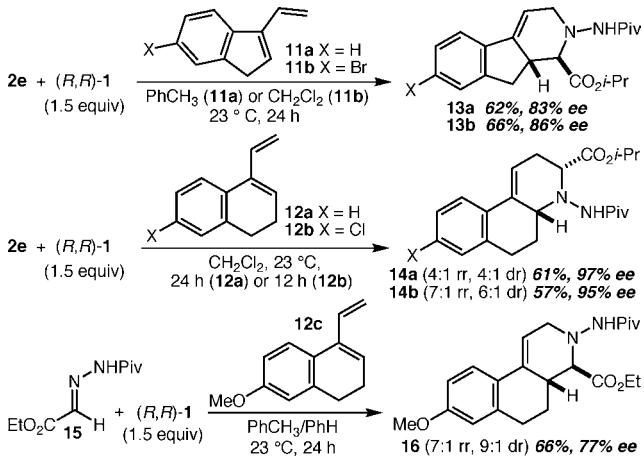
Aliphatic aldehyde-derived hydrazone **7** is also a successful substrate, albeit one that requires extended reaction times and/or elevated temperatures (Scheme 3). Despite the sluggish rate of these reactions, products **8**−**10** may be accessed with good to excellent yields and enantioselectivities. Aromatic aldehyde-derived hydrazones have thus far proven unreactive.

Scheme 3



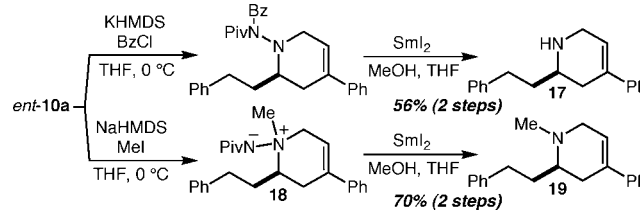
To further expand the scope with respect to the diene structure and to access more structural and stereochemical complexity in the products, dienes having the general structures **11** and **12** were investigated (Scheme 4). While such dienes have been extensively studied in Diels−Alder reactions (and with only two exceptions[5] react to give the regioisomer expected from stereoelectronic considerations), next to no information is available regarding the corresponding ADA reactions.[6] Reactions of dienes **11a** and **11b** with the complex formed from **2e** and (*R*,*R*)-**1** led to **13a** and **13b**, respectively. The products were formed with complete regio- and diastereoselectivity and in 83 and 86% ee, respectively. Interestingly, however, dienes **12a** and **12b** exhibited reversed regioselectivity, leading to **14a** and **14b**, respectively, as the major products of reactions that appear to be governed by the minimization of steric interactions in the initial C−C bond formation. While the regio- and diastereoselectivities in these reactions were not as high, the reactions are nevertheless preparatively useful, as **14a** was isolated pure in 61% yield and 97% ee and **14b** in 57% yield and 95% ee. Perhaps even more remarkably, a remote methoxy group reestablished the supremacy of electronic control in the dihydronaphthalene series, as the reaction of **12c** with the complex formed from **15** and (*R*,*R*)-**1** produced **16** (7:1 regioselectivity, 9:1 diastereoselectivity), albeit with reduced enantioselectivity.[7] After purification, **16** was isolated in 66% yield and 77% ee. Either regioisomer (**14** or **16**) is thus available based solely on variation of a remote substituent on the diene **12**, a phenomenon that appears to be without precedent in the long and illustrious history of the Diels−Alder reaction and its variants.

Scheme 4



Reductive cleavage of the N−N bond in the hydrazide products with SmI_2[8] requires prior acylation in a modification of the Friestad procedure.[9] Thus, benzoylation of *ent*-**10a** [prepared as in Scheme 3 using (*S*,*S*)-**1**] followed by reduction with SmI_2 gave **17** in 56% yield (Scheme 5). We also discovered an interesting alternative when an attempt to methylate the pivalamide nitrogen of *ent*-**10a** unexpectedly delivered **18**. Reduction of **18** with SmI_2 proceeded smoothly to give **19** in 70% overall yield.

Scheme 5



We have described the development of enantioselective (formal) ADA reactions with non-Danishefsky-type dienes promoted by a silicon Lewis acid. Both glyoxylate- and aliphatic aldehyde-derived hydrazones may be employed, and a reasonably wide scope with regard to diene structure has been demonstrated as well, giving access to a diverse array of piperidine derivatives.

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Supporting Information Available: Experimental procedures, characterization data, stereochemical proofs, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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