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An acyl-Claisen approach to the synthesis of lignans and substituted pyrroles*

David Barker‡, Benjamin Dickson, Nora Dittrich, and Claire E. Rye

School of Chemical Sciences, The University of Auckland, 23 Symonds St, Auckland, New Zealand

Abstract: The acyl-Claisen rearrangement, also called a zwitterionic aza-Claisen rearrangement, allows for the synthesis of 2,3-*syn*-substituted morpholine pent-4-eneamides with high levels of diastereoselectivity. A wide variety of alkyl and aryl substituents can be introduced with yields highly dependent on the stoichiometry of the Lewis acid catalyst. The use of these morpholine amides in the synthesis of the tetrasubstituted tetrahydrofuran lignans fragransin A_2, talaumidin, and galbelgin is summarized. The conversion of the Claisen-derived amides into aryl tetraline and 1,1-diarylbutanol lignans via alteration of the protecting groups is also described. Nucleophilic addition of an organometallic reagent to the morpholine amide followed by Wacker oxidation of the alkene gives highly substituted 1,4-diketones, which can be easily converted into fully substituted pyrroles.

Keywords: asymmetric synthesis; lignans; natural product synthesis; pyrroles; rearrangements.

INTRODUCTION

The Claisen rearrangement from the initial discovery in 1912 [1] has been widely used in the synthesis of many complex natural products [2,3]. From the original high-temperature thermal conditions used to rearrange aryl-allyl ethers, a large number of variants have been developed which allow the rearrangement of a wide variety of substrates under numerous conditions. The highly ordered transition state of the [3,3]-sigmatropic rearrangement generally leads to high levels of stereocontrol, especially when (*E*)-configured allylic groups are employed. Some of the most popular and well-known Claisen variants are the Ireland–Claisen [4], the Johnson–Claisen [5], and the Meerwein–Eschenmoser–Claisen [6]. In contrast to the classical reaction and these well-used variants, aza-Claisen rearrangements have been explored to much lesser extent, owing mainly to the more forcing conditions required (often >200 °C). However, significant rate improvement is seen and lower temperatures can be used when charged species are employed in aza-Claisen rearrangements. The rearrangement of amide enolates, for instance, occurs smoothly at 135 °C [7] (Scheme 1). Further improvements are seen in the rearrangements of *N*-allyl ammonium enolates, recently called an acyl-Claisen rearrangement [8]. These zwitterionic species, formed from the reaction of an allylic amine with a ketene, formed in situ from an carboxylic acid halide and base, rearrange at room temperature or below [9,10]. Often, higher levels of selectivity are seen in aza-Claisen rearrangements than their oxygen counterparts owing to the well defined (*Z*)-enolate geometry [7].

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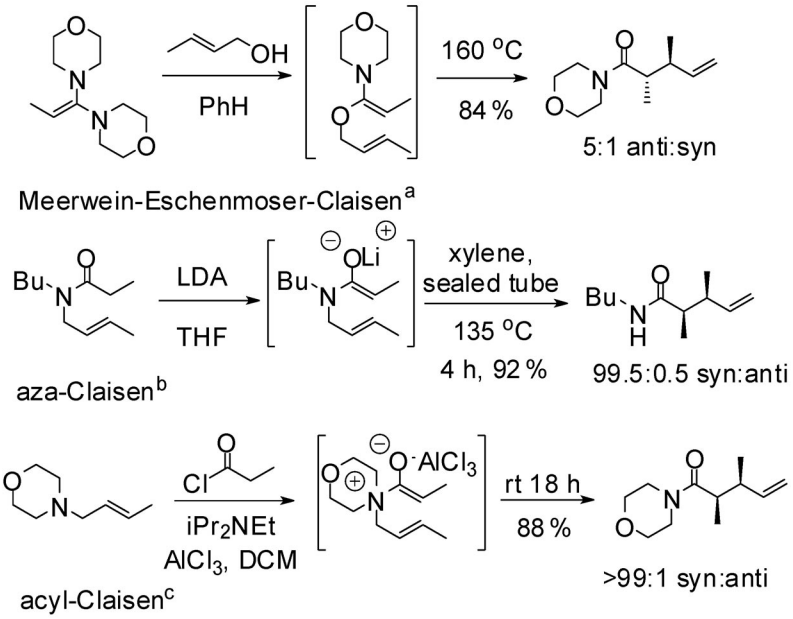
‡Corresponding author



Scheme 1 Comparison of Claisen variants giving amide products; [a]ref. [14], [b]ref. [7], [c]ref. [15].

We envisaged that the 2,3-disubstituted morpholine amides **1** derived from the acyl-Claisen rearrangement would be useful precursors for a wide range of five-membered heterocycles (Fig. 1). The morpholine of the amide should be easily substituted using an organometallic reagent to give ketones **2**, whilst the alkene could be manipulated in a variety of ways. In particular, the *syn* stereoselectivity of the amide would allow the synthesis of a number of tetrahydrofuran natural products which contain a *trans* relationship between the substituents at the 3- and 4-positions. We also envisaged that Wacker–Tsuji oxidation [11] of the terminal alkene of ketones **2** would give diketones **3**, which could be converted to highly substituted heterocycles under Paal–Knorr conditions [12,13]. The advantage of using diketones **3**, which contain a *trans*, rather than a *syn*, arrangement, between the 3- and 4-substituents, in the precyclized conformation, as precursors for pyrroles has previously been reported [16].

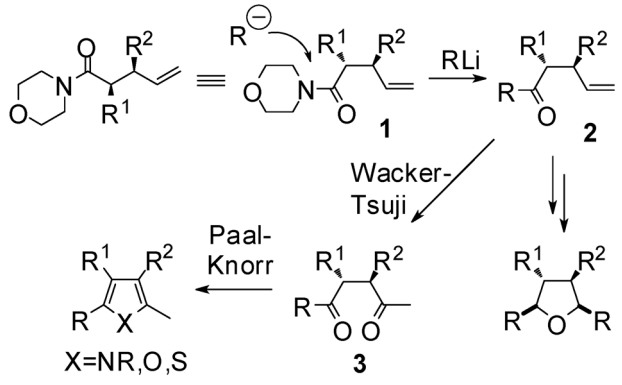
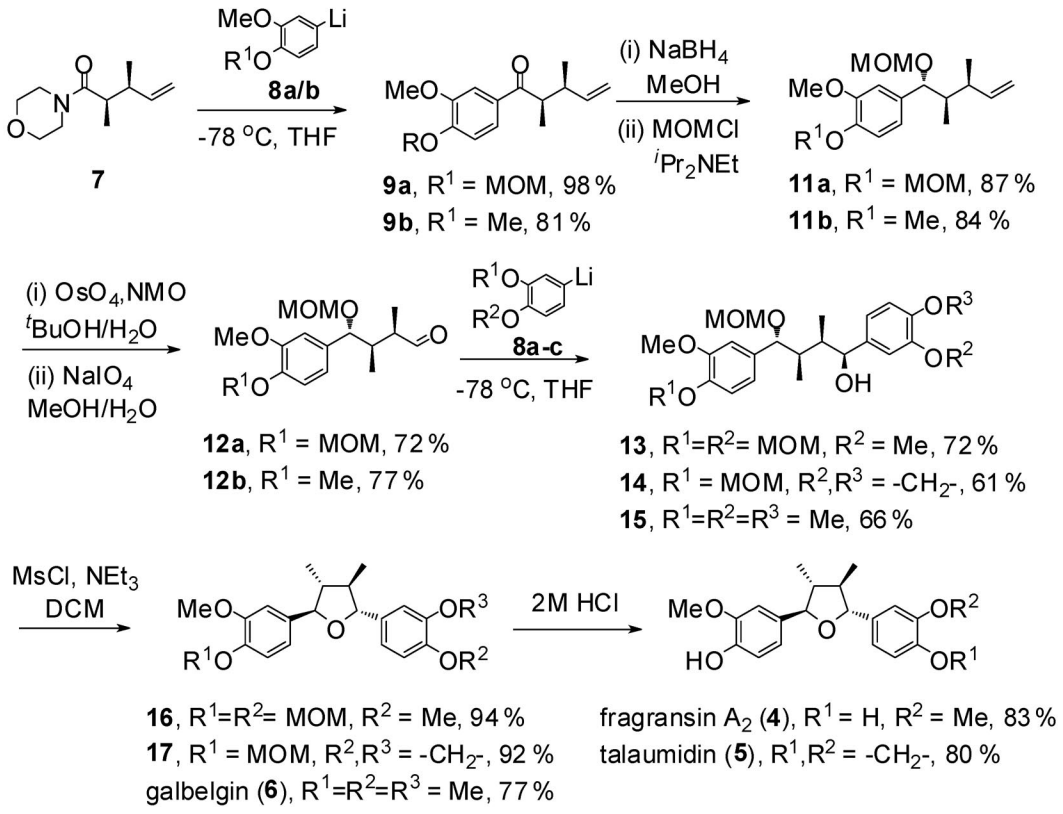


Fig. 1 Proposed application of morpholine amides to the synthesis of heterocycles.

SYNTHESIS OF TETRAHYDROFURAN LIGNANS

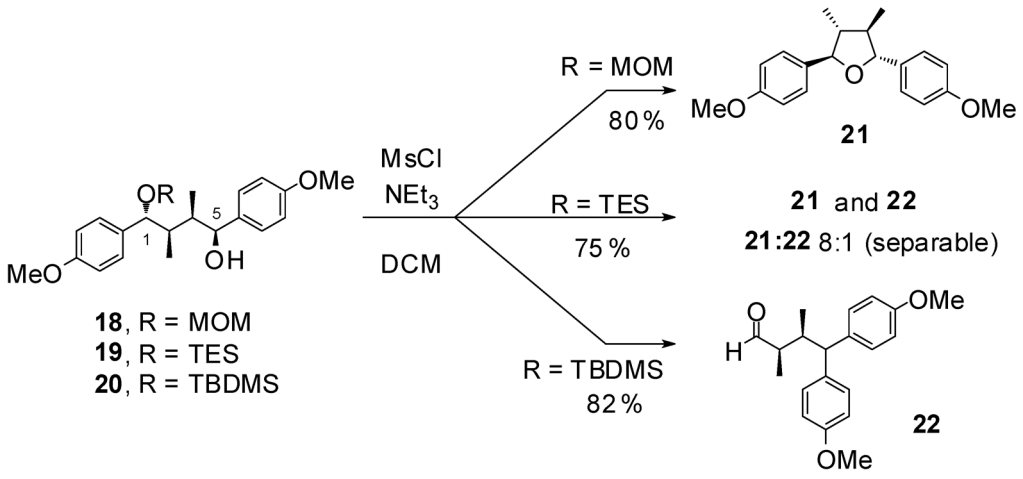
Tetrasubstituted tetrahydrofurans are a structural motif found in many natural products. One compound class containing this motif are the tetrahydrofuran lignans of which there are a large number of biologically active members [17,18], including fragransin A_2 **4** [19], talaumidin **5** [20], and galbelgin **6** [21]. In many cases, the stereochemistry of the substituents has been found to be important for biological activity [17]. We envisaged that by using a suitably substituted *syn*-disubstituted ketone **2**, the stereochemistry at the two chiral centers could then be used to control the subsequent synthetic steps, giving defined stereochemistry at the 2- and 5-positions in the final tetrahydrofuran. Our synthesis of lignans **4–6** began from the acyl-Claisen-derived *syn*-dimethyl morpholine amide **7** [13]. Whilst addition of Grignard reagents to amide **7** was ineffective, addition of aryl lithiates **8a/b** successfully gave ketones **9a/b** in excellent yields (Scheme 2). Reduction of ketones **9a/b** using $NaBH_4$ gave alcohols **10a/b** as single diastereoisomers, which were then protected as the methoxymethyl (MOM) ethers **11a/b**. Dihydroxylation of **11a/b**, using OsO_4, followed by oxidative cleavage using $NaIO_4$ gave aldehyde **12** in 72 and 77 % yields, respectively, over two steps. Whilst addition of Grignard reagents to aldehydes similar to **12** have been reported to give mixtures of diastereoisomers [22], we found that the addition of aryl lithiates **8a–c** to aldehydes **12** at –78 °C gave alcohols **13–15** as single isomers in good yields. Conversion of alcohols **13–15** into tetrahydrofurans **16**, **17**, and galbelgin **6** was achieved by methanesulfonyl chloride along with triethylamine. These conditions activate the alcohol, deprotect the alkyl MOM ether, and give the cyclized tetrahydrofuran **6**, **16**, and **17** in 77, 94, and 92 % yields, respectively, in a single synthetic step. Removal of the aryl MOM ethers of **16** and **17** using 2 M HCl gave fragransin A_2 **4** and talaumidin **5** in 83 and 80 % yields, respectively.



Scheme 2 Synthesis of fragransin A_2 **4**, talaumidin **5**, and galbelgin **6**.

SYNTHESIS OF ARYL TETRALINE AND DIARYL BUTANOL LIGNANS

We have previously shown [13] that alcohols that have the opposite stereochemistry at C-5 to alcohols **13–15**, undergo cyclization to give a mixture of the desired *trans*,*trans*,*cis* tetrahydrofurans and the unexpected all *trans* isomer. Therefore, in order to further explore the tetrahydrofuran-forming cyclization step, we wished to determine whether the C-5 mesylates formed retained the stereochemistry of the original alcohol or whether epimerization was occurring during formation. This required altering the C-1 MOM protecting group, as it participates in the cyclization under the mesylate-forming conditions. Model compounds were prepared where the C-1 ether was either a MOM **18**, triethylsilyl (TES) **19**, or *t*-butyldimethylsilane (TBDMS) **20** group (Scheme 4). Each were prepared from amide **7** in the same manner as shown in Scheme 2, using lithiated 4-bromoanisole as the aromatic component [23]. As expected, when MOM ether **18** was reacted with methanesulfonyl chloride, all *trans* tetrahydrofuran, dimethyl-4-*epi*-larreatricin **21**, was formed as the sole product in 80 % yield. Reaction of the TES ether **19** gave tetrahydrofuran **21** and aldehyde **22** in 67 and 8 % yields, respectively, with no mesylate formed. When the more acid-stable TBDMS ether **20** was used under the same conditions, only aldehyde **22** was formed in 82 % yield (Scheme 3).



Scheme 3 Synthesis of tetrahydrofuran **21** and aldehyde **22**.

We propose that the synthesis of aldehyde **22** involves initial formation of the quinoid intermediate **23**, however, in this case the generated HCl does not cleave the O–Si bond leading to the formation of an O-centered nucleophile, as occurs for the MOM ether **18**. Instead, *ipso* attack of adjacent aromatic carbon, via donation from the *para* methoxy group, on C-5 leads to the formation of cyclopentyl intermediate **24**. Cleavage of the O–Si bond and rearomatization then gives aldehyde **22** (Fig. 2).

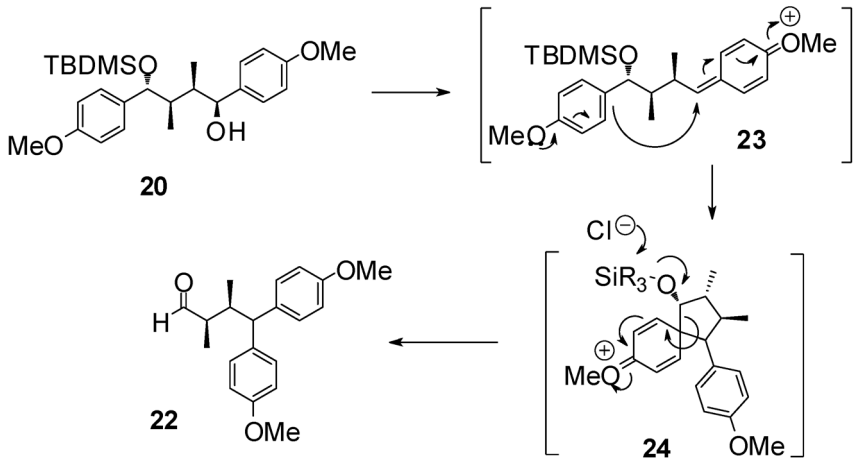
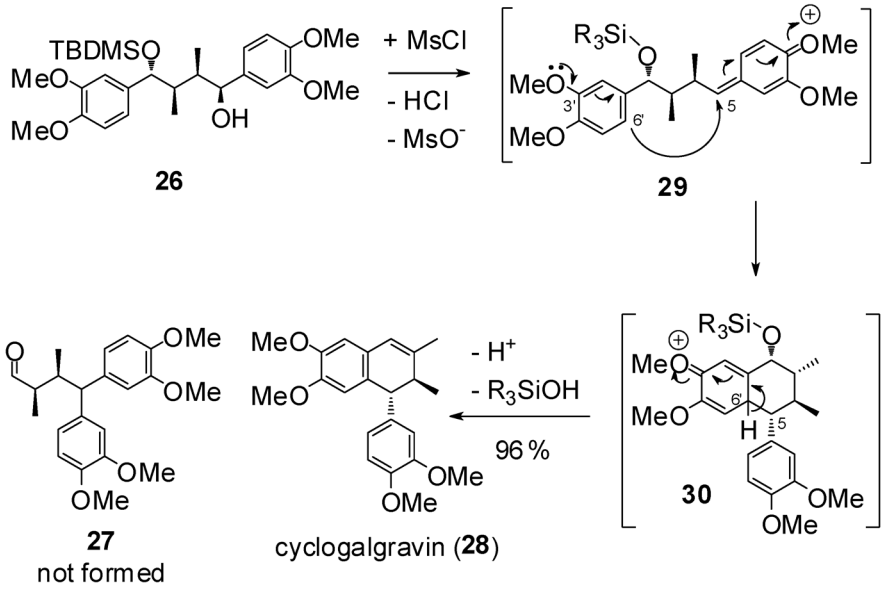


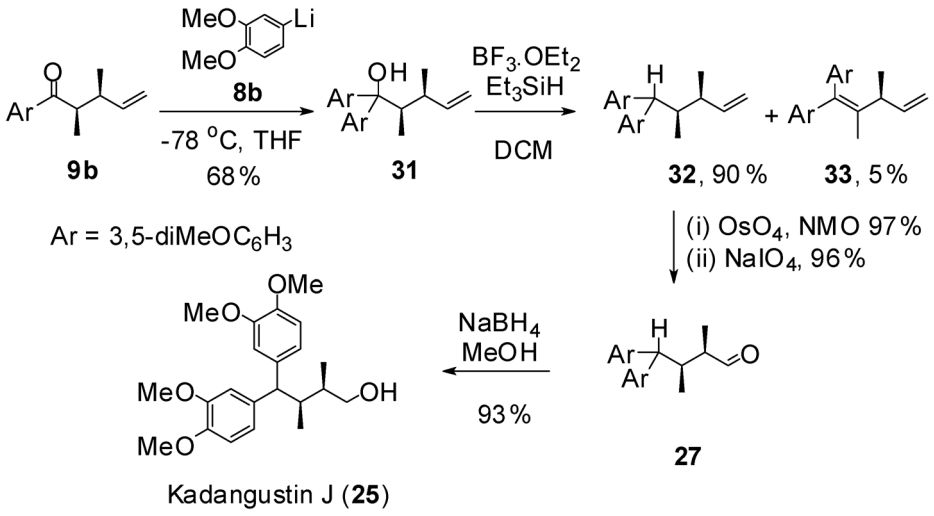
Fig. 2 Proposed mechanism for the synthesis of aldehyde **22**.

Owing to the similarity of aldehyde **22** to the recently isolated 1,1-diaryl butanol lignan kadangustin J **25**, we wished to see if this rearrangement process could be used to prepare such lignans. The TBDMS ether derivative of **15**, alcohol **26**, which contained the correctly substituted aromatic moieties was prepared from amide **7** using similar procedures as shown above [23]. When alcohol **26** was reacted with methanesulfonyl chloride and triethylamine in the same manner as the formation of aldehyde **22**, rather than aldehyde **27** being formed, the aryl tetraline lignan cyclogalgravin **28** was obtained in 96 % yield as a single diastereoisomer (Scheme 4). The synthesis of **28** can be explained firstly by the formation of quinoid intermediate **29**. The attack of C-6', which is *para* to the C-3' methoxy group, at C-5 then occurs, rather than *ipso* attack of C-1' seen in the formation of aldehyde **22**. The resultant intermediate **30** then rearomatizes and undergoes elimination of *tert*-butyldimethylsilanol to form cyclogalgravin **28**.



Scheme 4 Synthesis of cyclogalgravin **28**.

With the cyclization route giving aryl tetraline lignans and not the desired aldehyde **27**, an alternative strategy to kadangustin J **25** was designed. This initially involved the addition of lithiate **8b** to ketone **9b**, giving 1,1-diaryl alcohol **31** in 68 % yield (Scheme 5).



Scheme 5 Synthesis of kadangustin J **25**.

Alcohol **31** was dehydroxylated using a mixture of Et_3SiH and $BF_3{\cdot}OEt_2$ using dilute conditions in dichloromethane (DCM) and gave a 20:1 mixture of the desired alkane **32** along with dehydrated alkene **33** in 95 % overall yield. Dihydroxylation-oxidative cleavage of the terminal alkene of **32** then gave aldehyde **27** in 92 % yield. Reduction of aldehyde **27** using $NaBH_4$ gave kadangustin J **25** in 93 % yield. The ^1H and ^{13}C NMR data for synthetic **25** was identical to the reported data [24], thus determining the previously unknown stereochemistry of the two methyl substituents in the natural product to be *syn*.

acyl-CLAISEN SYNTHESIS OF 2,3-DIARYLPENT-4-ENE MORPHOLINE AMIDES

There are numerous five-membered heterocycles with aryl substituents at the 2- and 3-position, examples include tricuspidatol A **34** (Fig. 3) [25], ningalin B **35**, and lukianol A **36** [26].

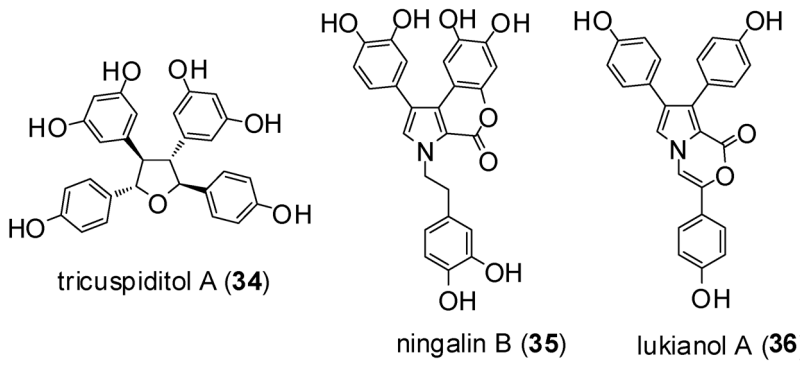
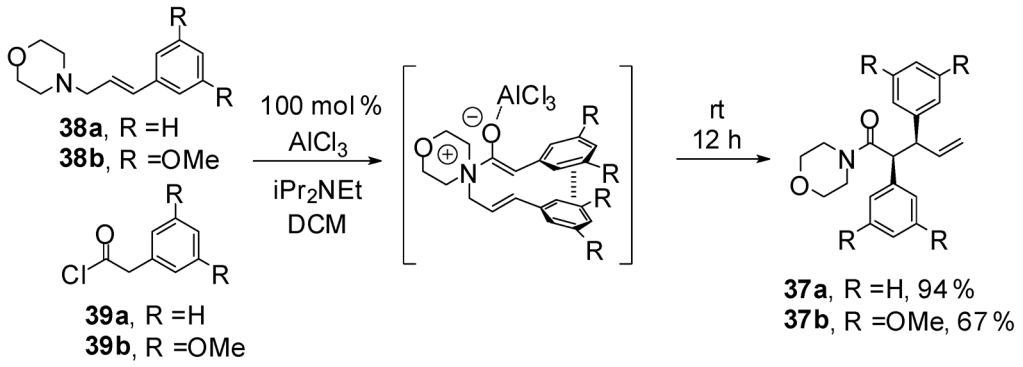


Fig. 3 Natural products with aryl substituents.

Whilst the acyl-Claisen rearrangement has been shown to be compatible for a range of allylic morpholines and acid chlorides, its application to the synthesis of 2,3-diarylpent-4-ene amides is yet to be explored. We initially wished to investigate whether diphenylamide **37a** could be prepared using cinnamyl morpholine **38a** and phenylacetyl chloride **39a**. The use of electron-rich allylic morpholines has previously been shown to give low yields when non-aryl acid chlorides were employed [8]. The reaction between **38a** and **39a** using 10–50 mol % $AlCl_3$ resulted in no reaction or only a trace of amide **37a** being obtained. However, when 100 mol % $AlCl_3$ was used, amide **37** was obtained in 94 % yield (Scheme 6).

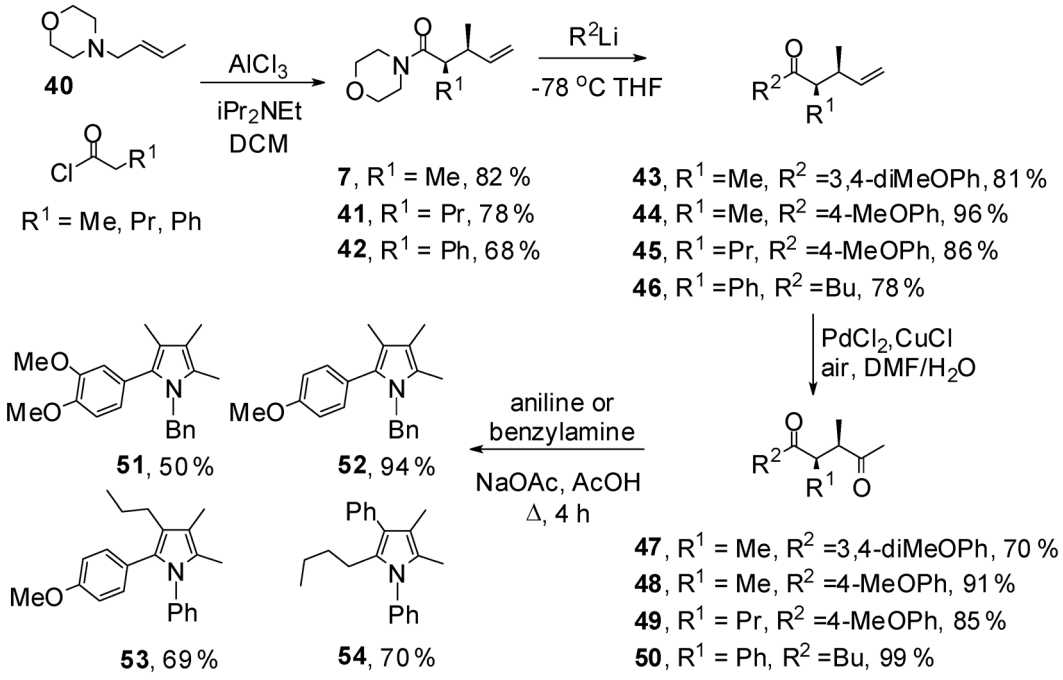


Scheme 6 acyl-Claisen synthesis of diarylamides **37a/b** highlighting proposed π–π interactions in the transition state.

A similar result was seen when the very electron-rich 3,5-dimethoxycinnamyl morpholine **38b** and 3,5-dimethoxyphenylacetyl chloride **39b** were employed, giving amide **37b** in 67 % yield but only when 100 mol % $AlCl_3$ was employed. To explore these results, the reaction in mono-aryl systems was further investigated. The reaction of phenylacetyl chloride **39a** with crotyl morpholine **40** was successful, giving amide **41** in 86 % yield (Scheme 7). However, the reaction of generally more reactive propionyl chloride with either of the cinnamyl morpholines **38a/b**, even at 100 mol % $AlCl_3$, resulted in only a trace of the corresponding amides. These results suggest that favorable π–π interactions between the two aryl groups in the chair-like transition state may help to facilitate the reaction of cinnamyl morpholines. The application of amides such as **37a/b** as precursors in the synthesis of natural products **34–36** and their analogues is currently being investigated.

SYNTHESIS OF HIGHLY SUBSTITUTED PYRROLES FROM acyl-CLAISEN-DERIVED AMIDES

There are numerous examples of highly functionalized and substituted pyrroles having potent biological activity. Examples include natural products such as **35** and **36** and members of the lamellarin family of pyrrole alkaloids [27] along with synthetic compounds, such as the cholesterol-lowering drug atorvastatin [28]. We decided to investigate whether acyl-Claisen-derived amides could serve as precursors to substituted pyrroles. Thus, a series of amides **7**, **41**, and **42** were prepared in good yields via reaction of crotyl morpholine **40** with propionyl, valeryl, or phenylacetyl chlorides, respectively. Amides **7**, **41**, and **42** were then treated with either *n*-butyllithium or aryl lithiums **8b/d**, giving alkyl or aryl ketones **43–46** in good to excellent yields. Wacker–Tsuji oxidation [11] using $PdCl_2$ and CuCl in a rapidly stirring mixture of DMF-water open to air gave diketones **47–50** in excellent yields (Scheme 7). Finally, condensation of diketones **47–50** with either aniline or benzylamine gave fully substituted pyrroles **51–54** in good to excellent yields. The ability of the acyl-Claisen rearrangement to



Scheme 7 acyl-Claisen synthesis of substituted pyrroles **51–54**.

introduce diverse substituents to these diketones thus allows the preparation of a wide variety of highly substituted pyrroles.

CONCLUSION

The acyl-Claisen rearrangement allows the synthesis of a diverse range of substituted amides. We have shown that the morpholine amide and terminal alkene functionalities can be easily utilized, giving access to a range of lignan natural products. We have also shown that the same acyl-Claisen-derived morpholine amides can serve as excellent precursors for the synthesis of poly-substituted aromatic heterocycles.

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