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Synthesis of 2,3-*syn*-diarylpent-4-enamides via acyl-Claisen rearrangements of substituted cinnamyl morpholines: application to the synthesis of magnosalicin

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ABSTRACT

The acyl-Claisen rearrangement of substituted phenylacetyl chlorides and cinnamyl morpholines gives 2,3-*syn*-diarylpent-4-enamides. Electron-rich cinnamyl morpholines containing alkoxy substituents only reacted with phenylacetyl chlorides; replacement of the phenylacetyl chlorides with alkyl acid chlorides in these reactions gave no rearranged products. Use of the morpholine amides generated in the synthesis of the natural tetrahydrofuran neolignan magnosalicin and tetraphenyl tetrahydrofuran is also reported.

The acyl-Claisen rearrangement is a room temperature variant of the Claisen rearrangement involving the rearrangement of *N*-allyl ammonium enolates.[1] These zwitterionic species, formed from the reaction of an allylic amine with a ketene, generated in situ from a carboxylic acid halide and base, rearrange at room temperature or below. When (*E*)-allylic amines are employed, 2,3-*syn*-disubstituted pentenamides are formed, often with much higher levels of selectivity than their oxygen counterparts due to the well defined (*Z*)-enolate geometry.[2] We have recently shown[3] that acyl-Claisen derived amides can be used in the stereoselective syntheses of a range of lignan natural products. There are no previous examples of acyl-Claisen rearrangements where both the acid chloride and allylic morpholine contained aromatic substituents, whilst the yields of reactions involving alkyl acid chlorides with cinnamyl morpholine **1a**, are lower than the non-aromatic counterparts.[1a] It should be noted that a silyl-modified Bellus–Claisen rearrangement has been used to synthesise 2,3-diphenyl substituted pentenamides, however, this proceeded to give a mixture of *syn* and *anti* isomers.[4] We herein report the acyl-Claisen rearrangement of substituted cinnamyl morpholines **1**, including electron-rich variants, and aromatic-containing acid chlorides **2**, to give aryl substituted morpholine pentenamides **3** with complete stereocontrol. The synthetic utility of these substituted morpholine pentenamides **3** in the synthesis of substituted tetrahydrofurans is also reported.

We previously found[3] that rearrangements involving non-aromatic components proceed, as reported,[1a] using 10 mol % of a Lewis acid catalyst, preferably $AlCl_3$ or $TiCl_4{\cdot}2THF$. However, when these conditions were used in the reaction between cinnamyl morpholine **1a** and phenylacetyl chloride (**2a**) none of the desired amide **3a** was formed. Alternative Lewis acids, $AlBr_3$, $YbOTf_3$ and $MgBr_2{\cdot}OEt_2$, were investigated, but they also failed to give any of the desired amide **3a**. Increasing the catalyst loading to 50% and finally 100% resulted in a significant improvement in yield, giving amide **3a** in 94% yield, exclusively as the *syn* diastereoisomer (Table 1, entry 1).[5] Use of stoichiometric Lewis acid in the reaction between morpholine **1a** and propionyl chloride (**2b**) gave amide **3b** in an improved 86% yield when compared to the catalytic conditions (Table 1, entry 2).

We next prepared alkoxy substituted, electron-rich, cinnamyl morpholines **1b–d** and phenylacetyl chlorides **2c–e** to test them in the acyl-Claisen rearrangement. Morpholines **1b** and **1c** were prepared from benzaldehydes **4a** and **4b**, firstly by Horner-Wadsworth-Emmons reactions to give acrylates **5a** and **5b**, both in quantitative yields (Scheme 1). Reduction of **5a** and **5b** using diisobutylaluminium hydride in CH_2Cl_2 gave alcohols **6a** and **6b** in 95% and 72% yields, respectively. Bromination of **6a** followed by substitution of the resultant bromide gave allylic morpholine **1b** in 49% yield over two steps. Bromination of **6b** proved problematic, therefore an alternative route via oxidation of **6b** with manganese dioxide followed by reductive amination using $NaCNBH_3$ gave allylic morpholine **1c** in an 87% yield over the two steps. Morpholine **1d** was prepared by selective demethylation[6] of **4b** to give diphenol **4c** in 75% yield; sequential alkylation of the two phenols

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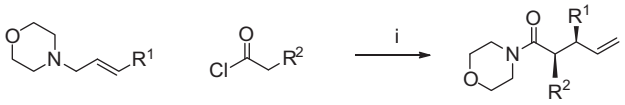
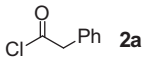
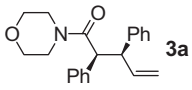
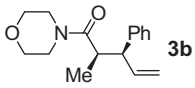
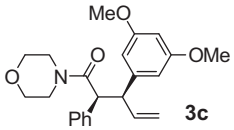
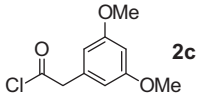
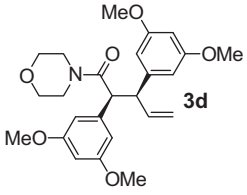
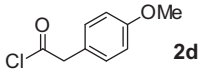
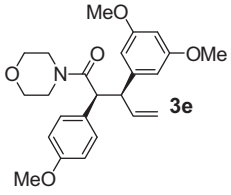
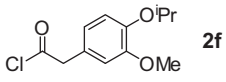
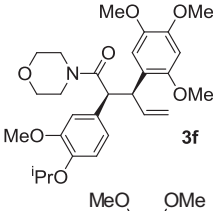
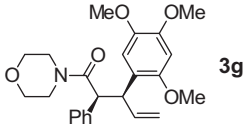
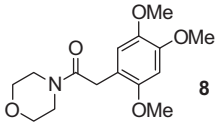
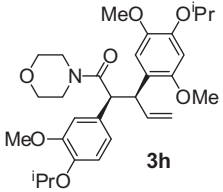
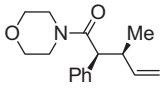
Table 1
Reagents and conditions: (i) **1** (1 equiv), **2** (1.2 equiv), Lewis acid (1 equiv), $^{i}Pr_2NEt$ (1.5 equiv), CH_2Cl_2, rt, 18 h

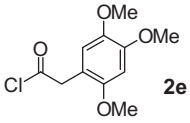
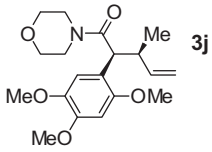
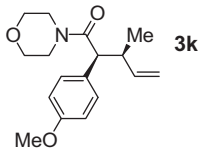


1a-e **2a-f** **3a-x**

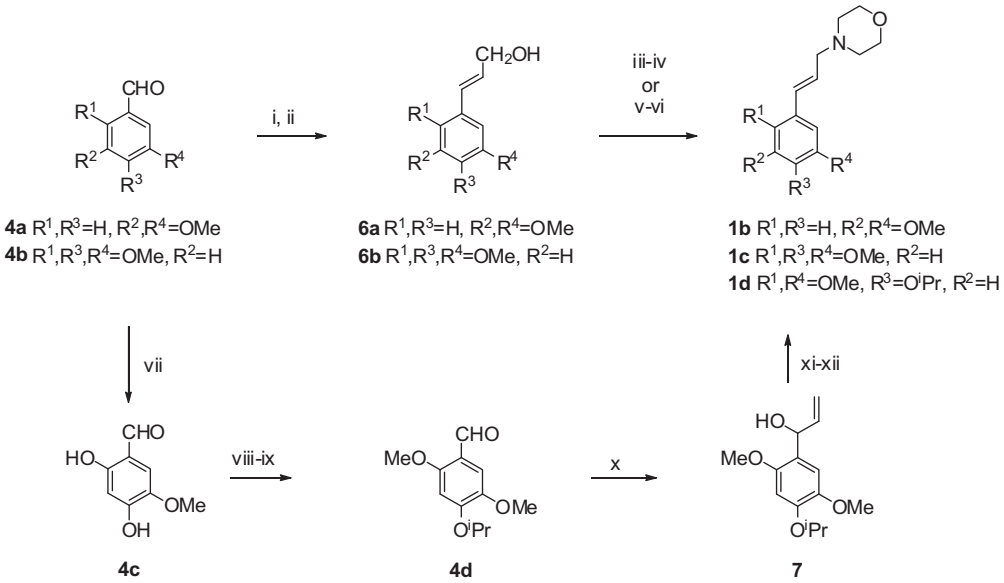
Entry	Allylic morpholine **1**	Acid chloride **2**	Amide **3**	Yield of **3** (%)
1	R^1 = Ph, **1a**	 **2a**	 **3a**	94[a]
2	**1a**	 **2b**	 **3b**	86[a]
3	**1b**	**2a**	 **3c**	40[b]
4	**1b**	 **2c**	 **3d**	63[a]
5	**1b**	 **2d**	 **3e**	83[b]
6	**1b**	**2b**	–	0[a, b]
7	**1c**	 **2f**	 **3f**	52[a]
8	**1c**	**2a**	 **3g**	40[a]
9	**1c**	**2b**	 **8**	0
10	**1d**	**2f**	 **3h**	79[a]
11	R^1 = Me, **1e**	**2a**	 **3i**	86[b]

(*continued on next page*)

Table 1 (*continued*)

Entry	Allylic morpholine **1**	Acid chloride **2**	Amide **3**	Yield of **3** (%)
12	**1e**	 **2e**	 **3j**	77[b]
13	**1e**	**2d**	 **3k**	73[b]

[a] $TiCl_4{\cdot}2THF$ was used.
[b] $AlCl_3$ was used.

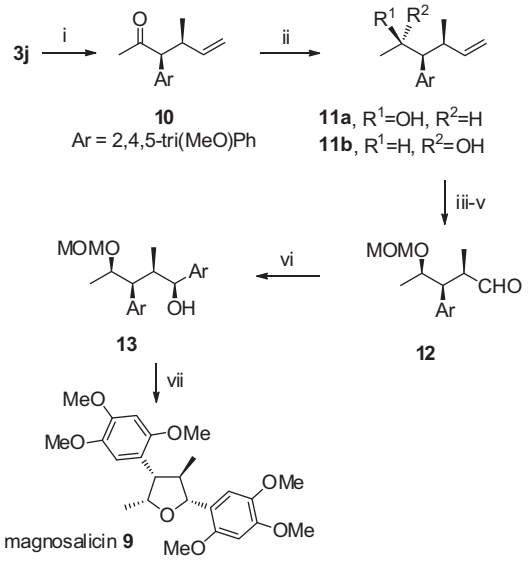


Scheme 1. Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$, K_2CO_3, THF, reflux, 20 h, **5a**,**5b** quant.; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 3 h, **6a** (95%), **6b** (72%); (iii) PBr_3, CH_2Cl_2, 0 °C to rt, 18 h; (iv) morpholine, NEt_3, CH_2Cl_2, 0 °C to rt, 18 h, **1b** (49%) from **6a**; (v) MnO_2, EtOAc, rt, 3 h; (vi) morpholine, $NaCNBH_3$, AcOH, MeCN, rt, 16 h, **1c** (87%) from **6b**; (vii) **4b**, $AlCl_3$, CH_2Cl_2, 72 h, 75%; (viii) ^{i}PrI, $NaHCO_3$, TBAI, DMF, 80 °C, 72 h, 58%; (ix) MeI, K_2CO_3, DMF, rt, 2 h, 86%; (x) vinylmagnesium bromide, THF, rt, 23 h, 88%; (xi) Ac_2O, pyridine, DMAP, THF, 0 °C to rt, 40 h; (xii) morpholine, $Pd(PPh_3)_4$, THF, 48 h, 34% from **7**.

gave benzaldehyde **4d** in 50% over two steps. Addition of vinylmagnesium bromide to aldehyde **4d** gave allylic alcohol **7** in 88% yield. Acetylation, followed by $Pd(PPh_3)_4$-mediated displacement of the resultant acetate[7] gave allylic morpholine **1d**. The known acid chlorides **2c**[8], **2d**[9] and **2e**[10] were prepared using literature conditions, whilst **2f** was prepared from commercially available homovanillic acid.[11]

The reaction of the allylic morpholine **1b** with phenylacetyl chloride **2a** gave amide **3c** in 40% yield (entry 3) and when acid chloride **2c** was used, amide **3d** was obtained in 63% yield (entry 4). Similarly when aromatic allylic morpholines **1b–d** were reacted with aryl substituted acid chlorides **2a**,**c–f**, 2,3-*syn*-diaryl amides **3e–h** were generated in 40–83% yields (entries 5–10). Notably, removal of the methyl or isopropyl ethers was not observed with any Lewis acid used. Reaction of propionyl chloride **2b**, or acetyl chloride, with allylic morpholines **1b-d** failed to give any of the rearranged amide products. In most cases starting materials were returned except in the case of **1c** where reaction with propionyl chloride **2b** gave only amide **8** formed via von Braun degradation.[12] Reaction of acid chlorides **2a**,**b**,**e** with crotyl morpholine **1e** proceeded as expected giving 2-aryl-3-methyl amides **3i–k** in 73–86% yields (entries 11–13). These results indicate that whilst **2a–f** react with both aryl and alkyl allylic morpholines **1a–e**, electron-rich substituted cinnamyl morpholines **1a-d** preferentially react with aryl substituted acid chlorides **2a**,**c–f**.

Polyoxygenated, electron-rich aromatic rings are found in a wide array of natural products including lignans,[13] the lamellarin family of pyrrole alkaloids[14] and resveratrol oligomers,[15] to name just a few. Magnosalicin (**9**) is a racemic tetrasubstituted tetrahydrofuran neolignan found in the buds of *Magnolia salicifolia* Maxim,[16] and has an unusual *cis, trans, trans*-2,4-diaryl substitution, rather than the more commonly found 2,5-diaryl substitution. Previously reported syntheses[17] of magnolsalicin (**9**) or analogues have predominately given the *trans,trans,trans* epimer of the natural product. Our synthesis of magnosalicin (**9**) began with the addition of methyllithium, at 0 °C in THF, to amide **3j** and gave ketone **10** in 52% yield. Reduction of ketone **10** with $NaBH_4$ at −78 °C gave alcohols **11a** and **11b** in a 9:1 ratio favouring the desired isomer **11a**. Protection of the alcohol **11a** as the MOM ether, followed by dihydroxylation and oxidative cleavage gave aldehyde **12** in 42%



Scheme 2. Reagents and conditions: (i) MeLi, THF, −78 °C to rt, 2 h, 52%; (ii) $NaBH_4$, MeOH, −78 °C to rt, 3 h, **11a** (83%), **11b** (9%); (iii) MOMCl, DIPEA, CH_2Cl_2, rt, 18 h, 68%; (iv) 10 mol % OsO_4, NMO, $^tBuOH/H_2O$, rt, 24 h; (v) $NaIO_4$, $MeOH/H_2O$, rt, 4 h, 62% over 2 steps; (vi) 2,4,5-trimethoxybromobenzene, BuLi, Et_2O, 0 °C, then add **12**, 3 h, 76%; (vii) MsCl, Et_3N, CH_2Cl_2, rt, 2 h, 62%.

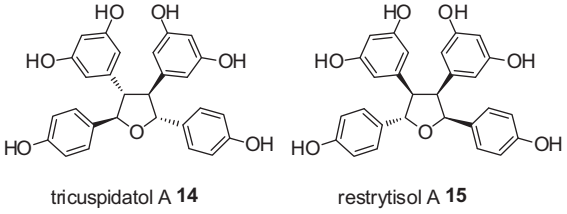
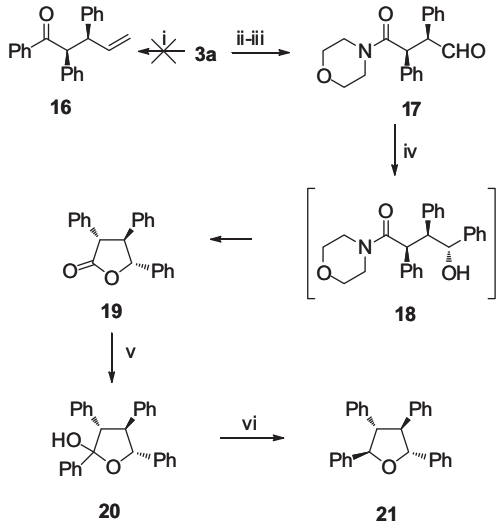


Figure 1. Resveratrol dimers tricuspidatol A **14** and restryisol A **15**.

yield over three steps. Addition of 2,4,5-trimethoxyphenyllithium (from the bromo compound) to aldehyde **12**, gave alcohol **13** in 76% yield. Finally, activation of alcohol **13** using mesyl chloride and Et_3N gave magnosalicin **9** in 62% yield (Scheme 2). The spectroscopic data of the isolated product matched reported literature data.[16]

Tricuspidatol A (**14**) and restrytisol A (**15**) are tetraaryl tetrahydrofurans, isolated from *Parthenocissus tricuspidata* (Fig. 1).[18,19] These compounds are antioxidants and are formed in a non-stereospecific manner from oxidative dimerisation of resveratrol.[20] We envisaged that 2,3-*syn*-diaryl amides could be used to form analogues of these natural products, using similar methodology to that used in the synthesis of magnosalicin **9**.

To test this proposal 2,3-diphenylpentenamide **3a** was reacted with phenyllithium in an attempt to form the ketone **16**. However under all the conditions tested[21] substitution of the morpholine group was not observed. In the belief that the neighbouring 2-phenyl group was sterically hindering the amide we attempted to circumvent this by conversion of the alkene in **3a** into aldehyde **17**, which it was hoped would be more susceptible to nucleophilic attack. Dihydroxylation of **3a**, followed by oxidative cleavage gave aldehyde **17** in 87% yield over two steps. Addition of phenyllithium to aldehyde **17** resulted in the formation of alcohol **18** which cyclised in situ to give lactone **19** in 69% yield, as a single diastereoisomer. Addition of phenyllithium to lactone **19** gave hemiketal **20** in 77% yield, which was then dehydroxylated using $BF_3{\cdot}OEt_2$ and Et_3SiH in CH_2Cl_2 at low temperature to give *trans,trans,trans*-2,3,4,5-tetraphenyltetrahydrofuran **21** in quantitative yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) PhLi or PhMgCl, THF or Et_2O, no reaction; (ii) 1 mol % OsO_4, NMO, $^tBuOH/H_2O$, rt, 24 h; (iii) $NaIO_4$, $MeOH/H_2O$, rt, 5 h, 87% over 2 steps; (iv) PhBr, *t*-BuLi, THF, −78 °C to rt, 2 h, 69%; (v) PhBr, *t*-BuLi, THF, −78 °C to rt, 2 h, 77%; (vi) $BF_3.OEt_2$, Et_3SiH, CH_2Cl_2, −78 °C for 1 h then −10 °C 3 h, quant.

In summary, the acyl-Claisen rearrangement of electron-rich, substituted cinnamyl morpholines **1** and substituted phenylacetyl chlorides **2** to give aryl substituted 2,3-*syn*-substituted pentenamides **3** can be achieved using stoichiometric Lewis acids. Amide **3j** was converted into the lignan magnolsalicin (**9**) in seven steps whilst amide **3a** was converted into tetraphenyl tetrahydrofuran **21** in five steps. Tetrahydrofuran **21** is a deoxygenated analogue of resveratrol dimers and this methodology should allow the synthesis of these natural compounds and their analogues.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.088. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

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3. (a) Rye, C. E.; Barker, D. *J. Org. Chem.* **2011**, *76*, 6636–6648; (b) Rye, C. E.; Barker, D. *Synlett* **2009**, 3315–3319.
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5. The *syn/anti* ratio was determined by ^1H NMR spectroscopy, where H-4 for the *syn* isomer is δ_H 0.2–0.5 ppm downfield of the corresponding signal in the *anti* isomer. General Procedure and selected data for the syntheses of amides **3**: To a stirred suspension of $AlCl_3$ or $TiCl_4{\cdot}2THF$ (1.0 mmol) in CH_2Cl_2 (5 mL) under an atmosphere of nitrogen, a solution of allylic morpholine **1** (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise, followed by DIPEA (1.5 mmol) dropwise. The resulting mixture was stirred at room temperature for 15 min, then a solution of acid chloride **2** (1.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. Aqueous NaOH solution (2 M, 10 mL) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography to give amides

3. Data for **3d**: δ_H (400 MHz, $CDCl_3$) 3.19–3.63 and (8H, 2 × m, N(CH_2CH_2)$_2$O) 3.64 (12H, s, 4 × OCH_3), 3.93 (1H, d, *J* = 10.5 Hz, 2-CH), 4.08–4.11 (1H, m, 3-CH), 5.08–5.16 (2H, m, 5-CH_2), 6.10 (1H, ddd, *J* = 6.8, 10.7, 17.3 Hz, 4-CH), 6.15 (2H, d, *J* = 2.2 Hz, 2 × Ar-H), 6.18 (2H, m, 2 × Ar-H), 6.24 (2H, d, *J* = 2.2 Hz, 2 × Ar-H), δ_C (100 MHz, $CDCl_3$) 42.5, 46.2, 66.5 and 66.8 (N(CH_2CH_2)$_2$O), 52.9 (C-2), 53.2 (C-3), 55.2, 55.3 (2 × OCH_3), 98.3 and 99.2 (Ar-CH), 106.7, and 107.0 (Ar-CH) 115.5 (C-5), 139.4 and 140.1 (Ar-C), 139.61 (C-4), 160.33 (Ar-C), 170.23 (C-1); IR ν_{max}/cm^{-1} 2960, 2838, 1637, 1456, 1150, 726; HRMS (ESI$^+$): found (MH$^+$): 422.2223 $C_{25}H_{32}NO_6$ requires 422.2224. Data for **3h**: δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.25–1.28 (12H, m, 2 × CH(CH_3)$_2$), 3.16–3.21 and 3.45–3.56 (8H, m, N(CH_2CH_2)$_2$O), 3.60 (3H, s, OCH_3), 3.70 (6H, s, 2 × OCH_3), 4.16 (1H, d, *J* = 10.8 Hz, 2-H), 4.34–4.41 (2H, m, 2 × $CH(CH_3)_2$), 4.47 (1H, dd, *J* = 7.2, 10.4 Hz, 3-H), 5.06–5.12 (2H, m, 5-CH_2), 6.18 (1H, ddd, *J* = 7.2, 10.4, 17.2 Hz, 4-H), 5.30 (1H, s, Ar-H), 6.39–6.58 (3H, m, Ar-H), 6.68–6.69 (1H, d, *J* = 2.0 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 22.1 (2 × CH(CH_3)$_2$), 42.5 and 46.2 (N(CH_2CH_2)$_2$O), 47.8 (C-3), 51.0 (C-2), 55.9, 56.0 and 57.0 (3 × OCH_3), 66.5 and 66.9 (N(CH_2CH_2)$_2$O), 71.2 and 72.0 (2 × $CH(CH_3)_2$), 102.5 (Ar-CH), 112.1 (Ar-CH), 115.1 (C-5), 115.2 (Ar-CH), 115.4 (Ar-CH), 120.9 (Ar-CH), 122.2 (Ar-C),130.6 (Ar-C), 139.7 (C-4), 144.4 (Ar-C), 145.8 (Ar-C), 146.2 (Ar-C), 149.9 (Ar-C), 151.5 (Ar-C), 171.1 (C-1); IR ν_{max}/cm^{-1} 2974, 2933, 1639, 1507, 1206, 1111; HRMS (ESI$^+$): found (MH$^+$): 528.2957 $C_{30}H_{42}NO_7$ requires 528.2956. Data for **3j**: δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* = 7.0 Hz, 3-CH_3), 2.93–3.03 (1H, m, 3-H), 3.12–3.20 and 3.41–3.74 (8H, m, N(CH_2CH_2)$_2$O), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.06 (1H, d, *J* = 10.4 Hz, 2-H), 5.00 and 5.10 (2 × 1H, dt, *J* = 1.0, 10.5 Hz, 5-CH_2), 5.91 (1H, ddd, *J* = 7.0, 10.5, 17.3 Hz, 4-CH), 6.50 (1H, s, Ar-H), 6.98 (1H, s, Ar-H); δ_C (100 MHz, $CDCl_3$) 16.8 (3-CH_3), 40.2 (C-3), 42.5 and 45.9 (N(CH_2CH_2)$_2$O), 44.4 (C-2), 56.1 (OCH_3), 56.4 (OCH_3), 56.5 (OCH_3), 66.7 and 66.9 (N(CH_2CH_2)$_2$O), 96.9 (Ar-CH), 111.4 (Ar-CH), 113.8 (C-5), 117.9 (Ar-C), 142.9 (C-4), 144.0 (Ar-C), 148.6 (Ar-C), 149.9 (Ar-C), 171.9 (C-1); IR ν_{max}/cm^{-1} 3080, 2965, 2851, 1634, 1513, 1203, 1110, 870; HRMS (ESI$^+$): found (MH$^+$): 350.1934 $C_{19}H_{28}NO_5$ requires 350.1962.

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21. We have attempted the substitution of the morpholine group in a number of 2-aryl morpholine amides with a variety of aromatic organometallic species and yields of the aryl ketone are generally <10%.