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Enantioselective organocatalytic aryloxylation of aldehydes with *o*-quinones

Felix A. Hernandez-Juan, Dane M. Cockfield and Darren J. Dixon*

School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

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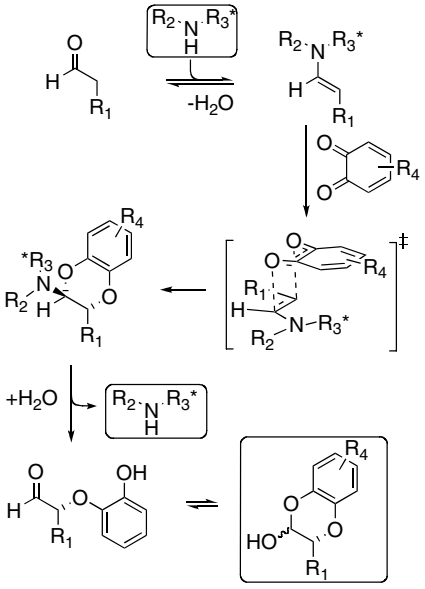
Abstract—An enantioselective organocatalytic inverse electron demand hetero Diels–Alder reaction of in situ generated enamines with *o*-quinone reagents is reported. The method, which is optimal in wet acetonitrile at ambient temperature, provides a new and direct asymmetric route to the aryl alkyl ether motif and an alternative metal-free strategy to S_N2 substitutions with phenolate nucleophiles.

Enantiopure aryl alkyl ether motifs, stereogenic at the aliphatic carbon of the ether linkage, are commonplace amongst a number of natural products,[1] commercial drugs and bioactive substances. Examples include the selective norepinephrine reuptake inhibitors fluoxetine,[2] reboxetine[3] and MKC-242.[4] Such motifs, whether targets in synthesis or intermediates in a synthetic transformation, are usually prepared by either Mitsunobu inversion using phenols and enantiomerically enriched alcohols or S_N2 displacement of a suitable leaving group by phenolate nucleophiles. Inevitably, this approach pivots on the preparation of the enantioenriched alcohol. Whether by enantioselective reduction of preformed prochiral ketones or epoxide opening strategies, the installation of this alcohol, and its subsequent transformation, can result in lengthy linear sequences.

We envisaged a more attractive and direct approach to this important structural motif originating from an asymmetric organocatalytic[5] hetero Diels–Alder reaction[6] of in situ generated enamines with *o*-quinone reagents.[7,8] As the enamines would originate from the parent carbonyl compound and *o*-quinones are readily prepared or are commercially available, this enantioselective aryloxylation strategy should offer an attractive and powerful alternative to existing methods.[9] The concept is shown in Scheme 1. We postulated that an appropriate chiral cyclic secondary amine catalyst would condense with an aldehyde component to make an enamine intermediate which could undergo a facially selective DA reaction.

In situ hydrolysis of the aminol motif in the direct Diels–Alder adduct would generate the aldehyde, which would



Scheme 1. Envisaged Diels–Alder reaction of *o*-quinones with enamines.

Keywords: Enantioselective organocatalysis; Enamine; *o*-Quinone; Diels–Alder; Aryloxylation.
* Corresponding author. Tel.: +44 161 2751426; fax: +44 161 2754939; e-mail addresses: darren.dixon@man.ac.uk; darren.dixon@manchester.ac.uk

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exist predominantly in the closed form, and release the chiral amine to continue the catalytic cycle. As the chemistry of such products is diverse, these compounds could serve as important intermediates in the synthesis of natural products and pharmaceutical targets alike.

Our investigations began by establishing proof of principle in the reaction of commercially available propionaldehyde **1** and *o*-chloranil **2** (Table 1). Using L-proline **4** (30 mol %) in chloroform at room temperature, 1 equiv of *o*-chloranil and 3 equiv of aldehyde, the reaction was stopped after 16 h. Work up and purification gave *o*-quinone adduct **3** in a yield of 53% (entry a). The enantiomeric excess of **3** (determined on the reduced derivative by chiral stationary phase HPLC) was 34% in favour of the *S*-enantiomer.[10] Having established proof of principle, successive rounds of catalyst screening (Fig. 1) were undertaken with the aim of improving enantioselectivity in the reaction (Table 1).

Initially, a range of L-proline amide derivatives (**5**–**7**) was investigated. Although the size and structure of the amide function varied widely, the sense and magnitude of enantiocontrol remained essentially the same as L-proline **4** in all cases (entries b–d). Next, pyrrolidine diphenyl methanol **8**, was investigated.[6a] No product was observed in the reaction mixture (entry e). Accordingly, our attention was turned to the use of enantiopure imidazolidinones (**9**–**11**). These have proven to be organocatalysts for promoting the enantioselective addition of nucleophilic reagents and conjugated diene reagents to α,β-unsaturated carbonyl compounds.[11] Pleasingly, in the addition of propionaldehyde to *o*-chloranil, all imidazolidinone catalysts gave rise to product materials. With benzyldimethyl imidazolidinone **9** (entry f) the enantioselectivity was only moderate. With benzyl *tert*-butyl imidazolidinone **10** (entry g)[12] the enantioselectivity was 82%, but the reaction was particularly sluggish. However, using the less sterically demanding *tert*-butyl imidazolidinone **11** (entry h),[13] a good reaction yield and a high enantioselectivity in favour of the *S*-enantiomer, was obtained.

Having screened for enantiomeric excess, yield optimisation was undertaken using champion catalyst *tert*-butyl imidazolidinone **11** (entries h–k). A range of reaction conditions was tested using 3 equiv of aldehyde, 1 equiv of *o*-chloranil, and 10% catalyst at 26 °C. Good enantiocontrol (80–84% ee) and yields (72–77%) were witnessed with a variety of typical laboratory solvents (such as chloroform, toluene and acetonitrile), but in terms of

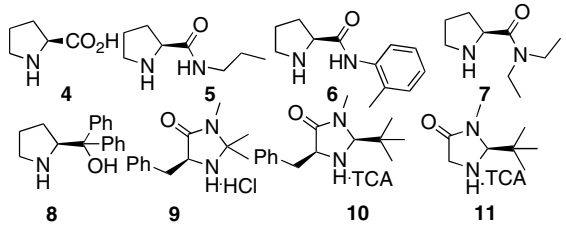
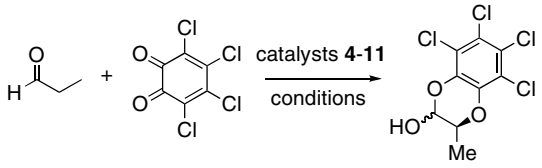


Figure 1.

Table 1. Screen of potential catalysts and conditions



Entry	Cat. (%)	Solvent	*T* (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
a	**4** (30)	$CHCl_3$	rt	16	53	34
b	**5** (30)	$CHCl_3$	rt	16	42	33
c	**6** (30)	$CHCl_3$	rt	16	34	33
d	**7** (30)	$CHCl_3$	rt	16	36	33
e	**8** (30)	$CHCl_3$	rt	16	—	—
f	**9** (30)	$CHCl_3$	rt	16	42	40
g	**10** (10)	$CHCl_3$	rt	120	73	82
h	**11** (10)	$CHCl_3$	26	16	77	84
i	**11** (10)	CH_3CN	26	24	73	82
j	**11** (10)	Tol	26	24	72	80
k	**11** (10)	CH_3CN/H_2O 9:1	26	6	75	80

[a] Determined by chiral stationary phase HPLC on the reduced products (see Supplementary data).
[b] Isolated yield after chromatography on silica gel.

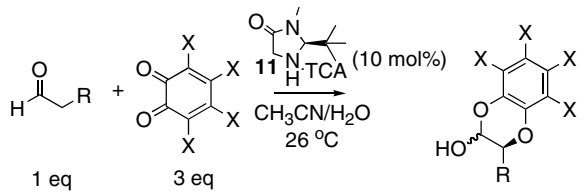
reaction speed the preferred solvent was wet acetonitrile. It is worth noting that these reactions are self-indicating, turning from deep red to pale yellow when complete.

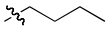
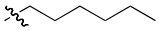
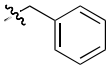
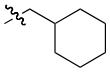
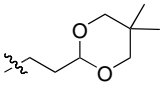
Having identified catalyst **11** and optimised the reaction conditions, a screen of commercially available, or readily prepared aldehydes in the reaction with *o*-chloranil was undertaken (Table 2). Using wet acetonitrile as solvent, short and long linear aldehydes and β-branched systems all performed well. Additionally, aldehydes bearing remote functionality also partook in the reaction. Products **12**–**17** were generated in yields ranging from 68–75% and with enantioselectivities from 75 to 81% ee. Additionally, *o*-bromanil reacted with propionaldehyde in an identical fashion and afforded adduct **18** in an unoptimised 52% yield and 79% ee (entry h).

The stereochemical outcome of the reaction is consistent with a favoured attack of the *o*-quinone reagent to the less hindered face of the in situ generated enamine, as shown in Figure 2. Accordingly, the *tert*-butyl group is responsible for fixing the conformation and providing the facial bias on approach of the *o*-quinone.

The Diels–Alder adducts, **3** and **12**–**18**, are versatile intermediates in synthesis. For example compounds **3** and **12** were converted into 2,3-dihydro-benzo[1,4]dioxine products **21** and **22** in an efficient two step process. Thus, **3** and **12** were reduced to the hydroxy phenols, **19** and **20**, respectively, using sodium borohydride in ether/methanol at room temperature. Subjection of these diols to Mitsunobu[14] conditions yielded 2,3-dihydro-benzo[1,4]dioxine products **21** and **22** in a high yield (Scheme 2). The ee of **21** was increased to >98% by recrystallisation and X-ray diffraction on a single crystal allowed the determination of the absolute stereochemistry as (*S*).

Table 2. Reaction scope



Entry	R	X	Time (h)	Product[a]	Yield[b] (%)	ee[c] (%)
a		Cl	6	**3**	75	80
b		Cl	36	**12**	73	80
c[d]		Cl	36	**13**	75	80
d		Cl	48	**14**	75	77
e		Cl	48	**15**	68	81
f		Cl	72	**16**	74	~80[e]
g		Cl	72	**17**	73	75
h[f]		Br	24	**18**	52	79

[a] Determined by chiral stationary phase HPLC on the reduced products (see Supplementary data).
[b] The (*S*)-stereochemistry of **3** was determined by X-ray analysis on a single crystal of a derivative;[10] others by analogy.
[c] Isolated yield after chromatography on silica gel.
[d] 20 mol % of **11** was used.
[e] After exhaustive chiral stationary phase HPLC analysis, near complete resolution of the enantiomers suggested an enantiomeric excess of ca. 80%.
[f] Carried out using *o*-bromanil and 10% of catalyst **11** in $CHCl_3$.

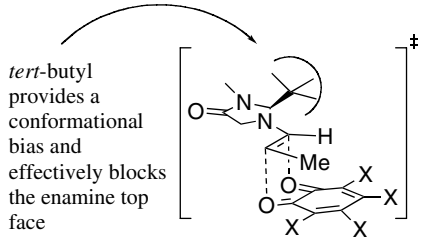
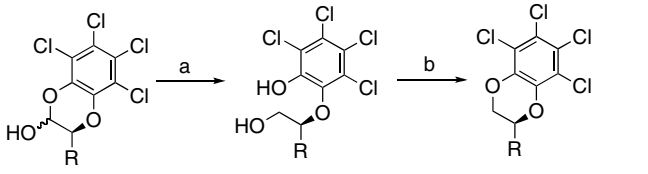


Figure 2. Postulated origin of stereocontrol.



Scheme 2. Reagents and conditions: (a) $NaBH_4$ (5 equiv), Et_2O/MeOH, rt, 30 min; (b) PPh_3 (1.2 equiv), DEAD (1.2 equiv), THF, rt, 24 h.

In conclusion, a direct enantioselective organocatalytic aryloxylation of aldehydes using an inverse electron demand hetero Diels–Alder reaction of in situ generated enamines and *o*-quinone reagents is described. Further investigations and applications in this field are ongoing and results will be reported in the near future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet 2006.12.140.

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