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**NHC-Catalysed Enantioselective Intramolecular Formal [4+2] Cycloadditions using Carboxylic Acids as Azolium Enolate Precursors**

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ABSTRACT

An NHC-catalysed intramolecular formal [4+2] cycloaddition protocol using carboxylic acid starting materials containing a tethered enone is reported. Optimisation studies using a model substrate showed that the use of the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) for in situ preparation of a mixed anhydride was necessary for effective catalysis, leading to highest product yield and stereoselectivity. Using this protocol, a range of dihydrobenzofurans were accessed in moderate to high yield, and with high to excellent diastereo- and enantioselectivity (up to > 95:5 dr and > 99:1 er). This methodology was extended to the synthesis of syn-dihydroychromone and syn-dihydropyrane derivatives in moderate to high yield and with excellent diastereo- and enantioselectivity.

Dedication: This manuscript is dedicated to Professor Steve Davies to celebrate his many outstanding achievements throughout his illustrious career in academia and as an entrepreneur. As a friend, mentor and advisor he has continually been an inspiration.

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1. Introduction

Azolium enolates are powerful synthetic intermediates that can undergo a wide range of enantioselective reactions. Such species are readily generated from an NHC through reaction with a variety of substrates, such as disubstituted ketenes, aldehydes in combination with an external oxidant, activated esters, and α-functionalised aldehydes such as enals, α-halo and α-aryloxy aldehydes. A range of enantioselective reactions have been developed with azolium enolates, however the most common applications involve intermolecular formal [4+2] cycloaddition reactions with reactive Michael acceptors such as enones.

Despite their utility, one key remaining challenge in this area is to identify bench stable, readily available and inexpensive azolium enolate precursors. In this regard, carboxylic acids potentially present an ideal profile. While carboxylic acids have been extensively used in Lewis base catalysis using isothiourea-, cinchona alkaloid- and DMAP-derived catalysts for the generation of C1-ammonium enolates through in situ formation of an efficient acylating agent such as a mixed anhydride, this concept remains relatively underexplored in NHC-catalysed processes. In this area, only a limited number of publications report the use of carboxylic acids to generate azolium enolate precursors and their use in intermolecular formal [4+2] cycloadditions. A seminal report published in 2014 by Scheidt and coworkers demonstrated the use of carboxylic acids toward the synthesis of dihydroquinolones 4 (Scheme 1a). In situ conversion of the carboxylic acid substrate was achieved using CDI in the presence of imidazole and Cs$_2$CO$_3$ with NHC addition, followed by deprotonation providing the azolium enolate. Subsequent enantioselective reaction with an aza-orthoquinone methide, produced in situ from an N-Boc 2-aminobenzyl chloride derivative 2, gave heterocycle 4 in excellent yield and stereoselectivity. Building upon this work, in 2015 Ye and coworkers reported the synthesis of syn-dihydropyrane derivatives in excellent yield and enantioselectivity, by utilising a limited range of arylacetic acids bearing electron donating aryl substituents (2-, 4-, 2,4-(MeO)$_2$C$_6$H$_4$, 4-MeC$_6$H$_4$) in combination with α,β-unsaturated γ-ketoesters 6 as Michael acceptors (Scheme 1b). In this process, the use of pivaloyl chloride in the presence of iPr$_2$NEt led to the in situ generation of a mixed acylamide as the acylating agent, with subsequent azolium enolate formation and formal [4+2] cycloaddition leading to the observed products. Building upon these precedents, we considered the potential for an NHC-catalysed intramolecular formal [4+2] cycloaddition process using carboxylic acids bearing a pendant enone as potential azolium enolate precursors (Scheme 1c). While related processes from carboxylic acids have been developed using tertiary amine Lewis bases, to the best of our knowledge this would represent a new avenue in NHC catalysis. Herein we report the enantioselective NHC-catalysed synthesis of a number of heterocycles using this protocol in good to excellent yields and stereosecontrol (up to 94% yield, > 95:5 dr and > 99:1 er).
NHC-catalysed azolium enolates from carboxylic acids

Previous work: a) Scheldt et al., 2014:

\[
\begin{align*}
R^1 & \text{COOH} \\
\text{R}^2 & \text{NR}^3 \text{N}^5 \text{BF}_4
\end{align*}
\]

1 (1.0 equiv)  
(R)-precat 3 (20 mol%)  
CDI (2.0 equiv)  
Imidazole (0.6 equiv)  
\( \text{CS}_2\text{CO}_3 \) (2.5 equiv)  
CPME, 4 °C, 15 h

b) Ye et al., 2015:

\[
\begin{align*}
\text{Ar-} & \text{OH} \\
\text{R}^1 & \text{O}^2\text{C} \\
\text{R}^2 & \text{N}^5 \text{BF}_4
\end{align*}
\]

5 (2.0 equiv)  
(i) i-ButOC\(_\text{Cl}\) (2.2 equiv)  
\( \text{Pr}_{2}\text{NEt} \) (3.0 equiv)  
CH\(_2\)Cl\(_2\), 10 °C, 30 min 
(ii) 10 (10 mol%)  
\( \text{Pr}_{2}\text{NEt} \) (2.0 equiv)  
-10 °C, 24–48 h 
8 (1.0 equiv)  
\( \text{Pr}_{2}\text{NEt} \) (2.0 equiv)  
-10 °C, 24–48 h

Table 1. Reaction optimisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Nucl (equiv)</th>
<th>Product</th>
<th>dr(^\text{a})</th>
<th>Yield</th>
<th>er(^\text{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isopropyl chloroformate (2.0)</td>
<td>BnNH(_\text{excess})</td>
<td>11</td>
<td>&gt; 95:5</td>
<td>67%</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>2</td>
<td>2,4,6-TCBC (1.1)</td>
<td>BnNH (1.5)</td>
<td>11</td>
<td>&gt; 95:5</td>
<td>61%</td>
<td>&gt; 99:1</td>
</tr>
<tr>
<td>3</td>
<td>2,4,6-TCBC (1.1)</td>
<td>Morpholine (1.5)</td>
<td>12</td>
<td>&gt; 95:5</td>
<td>73%</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-TCBC (1.1)</td>
<td>Morpholine (1.5)</td>
<td>12</td>
<td>&gt; 95:5</td>
<td>94%</td>
<td>97:3</td>
</tr>
</tbody>
</table>

TCBC = trichlorobenzyl chloride. [a] Determined by \( ^1 \text{H} \) NMR spectroscopic analysis of the crude reaction. [b] Determined by chiral HPLC analysis. [c] (i) and (ii) at 0 °C for 24 h. [d] (ii) at 0 °C for 24 h and (iii) at 0 °C for 4 h.

2. Results and Discussion

2.1. Model substrate reaction optimisation

The enantioselective cyclisation of enone-acid 9, previously investigated using other types of tertiary amine Lewis base catalysts,[8] was chosen as the model system for reaction optimisation.[9] The initial focus aimed to identify the optimal reagent for \textit{in situ} carboxylic acid derivatization in an NHC-catalysed intramolecular cyclisation protocol, with the initial [6,5]-fused dihydropyranone product ring-opened \textit{in situ} using an amine to facilitate isolation (Table 1). A series of reagents (pivaloyl chloride, EDCI, EDCI and HOBt, Mukaiyama reagents,[10] CDI, DCC, HATU) were all tested to facilitate the \textit{in situ} formation of reactive acylating agents from enone-acid 9. However, in all cases only low product yields (< 15%) were observed (See ESI for details). More encouraging results were obtained using isopropyl chloroformate, with dihydrobenzofuran 11 isolated in 67% yield, > 95:5 dr and > 99:1 er, after addition of benzyamine (Table 1, Entry 1). The (2S,3R)-configuration within 11 was identified by comparison of both specific rotation value and HPLC analysis to the literature.[6] Disappointingly, attempted repetition led to significant inconsistencies with variable product yields and er observed, indicating that chloroformates were not a reliable reagent for this system. As an alternative, the use of 2,4,6-trichlorobenzyl chloride (2,4,6-TCBC), widely known as the Yamaguchi reagent,[7] was explored at 0 °C (Table 1, Entries 2–4). Upon addition of benzylamine as the nucleophile, dihydroxyphane 11 was obtained in 61% yield, > 95:5 dr and > 99:1 er (Table 1, Entry 2). Changing the nucleophile to morpholine, and decreasing the temperature of the annulation and ring-opening steps to 0 °C, led to formation of dihydroxyphane 12 with consistent results (Table 1, Entry 3). Decreasing the reaction time of the ring-opening step to 4 h gave

2.2. Enone-acid scope and limitations

The scope of this process was examined, with variation of the enone substituent first probed (Table 2). Halogen substituents on the aryl group of the enone were readily incorporated, with dihydrobenzofuran derivative 19 (R = 4-BrC\(_6\)H\(_5\)) obtained in excellent 72% yield, > 95:5 dr and 96:4 er. Product 20 (R = 4-ClC\(_6\)H\(_5\)) was prepared in 74% yield and excellent > 95:5 dr and 94:6 er. Similarly, 21 (R = 4-F,C\(_6\)H\(_5\)) was formed in excellent > 95:5 dr and 93:7 er, but in reduced but still synthetically useful 55% yield. The lower yield for 21 can be accounted for by the observation of unknown side-products as identified by \( ^1 \text{H} \) NMR spectroscopic analysis of the crude reaction product. Interestingly, a significant decrease in yield as well as diastereo- and enantiocontrol was observed when electron donating substituents were incorporated on the aromatic group within the enone. For example, when enone-acid 16 (R = 4-MeC\(_6\)H\(_5\)) was used, 22 was formed in 90:10 dr, with purification giving an inseparable 91:9 mixture of diastereoisomers in 54% yield with 83:17 er for \textit{cis}-22. Product 23 (R = 4-MeO,C\(_6\)H\(_5\)) was obtained in 84:16 dr and in 51% yield as an inseparable 92:8 mixture of diastereoisomers after purification. Lower enantiocontrol was also observed, with \textit{cis}-23 obtained in 83:17 er. Finally, application of an alkyl enone (Me substituent) led to ≤ 5% conversion to product 24 by \( ^1 \text{H} \) NMR spectroscopic analysis of the crude reaction product, and was not isolated.
addition), with the majority focusing exclusively upon [6,5]-fused ring products (through a formal 5-exo-trig Michael addition). As a test substrate, the cyclisation of enone-acid 28 to prepare chromene derivative 29 was investigated. Treatment of 28 with 2,4,6-TCB, followed by precatalyst 10 and Pr2NEt, gave the desired isolable chromene 29 in 72% yield, >95:5 dr and 99:1 er (Scheme 2a), with the absolute configuration assigned by comparison to the literature of both specific rotation value and HPLC analysis. To broaden the scope of this methodology, the cyclisation of the non-benzannulated enone-acid 30, which was accessed in 4 steps from tert-butyl acrylate and buten-1-ol, was investigated. In this case, treatment of 30 with 2,4,6-TCB, followed by precatalyst 10 and base, gave the desired cis-tetrahydropyran derivative 31 in 50% yield, >95:5 dr and >99:1 er (Scheme 2b). The relative and absolute configuration within 31 was assigned by analogy to 29.

Table 3: Scope: variation of the nucleophile component

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a</td>
<td>69%</td>
<td>90:10 dr</td>
<td>93:7 er</td>
</tr>
<tr>
<td>27a</td>
<td>60%</td>
<td>95:5 dr</td>
<td>96:4 er</td>
</tr>
</tbody>
</table>

Dr determined by 'H NMR spectroscopic analysis of the crude reaction. Er determined by chiral HPLC analysis. Isolated yield. TCB = trichlorobenzoyl chloride. | Each is isolated as a 91:9 mixture of diastereoisomers. | Isolated as a 92:8 mixture of diastereoisomers. | Use of 20 mol% precatalyst 10, 24 could not be isolated.

**2.3. Nucleophile scope**

The scope of this transformation was further evaluated through variation of the nucleophile used to promote ring-opening of the initially formed dihydropryanone product from cyclisation of 9 (Table 3). The use of either piperidine or benzylamine led to similar results, giving 25 and 11, respectively, in good yield and excellent diastereo- and enantiocontrol. The use of diethylamine gave 26 in 69% yield and excellent 90:10 dr and 93:7 er. The use of MeOH, in combination with catalytic DMAP, led to the formation of methyl ester 27 in 60% yield, 95:5 dr and 96:4 er, with the (25R)-absolute configuration assigned by comparison with literature HPLC analysis and specific rotation values.

**2.4. Extension to 6-membered ring cyclisation**

Having demonstrated the viability of this strategy for the preparation of a small range of dihydrobenzofurans, the extension of this protocol toward the formation of 6-membered ring products was investigated (Scheme 2). To date, relatively few reports have been published on organocatalytic intramolecular formal [4+2] cycloadditions for the generation of [6,6]-fused ring systems (through a formal 6-exo-trig Michael
2.5. Proposed Mechanism and stereochemical model

A proposed mechanism for the formation of the observed products (illustrated for dihydrobenzofuran formation) involves initial formation of mixed anhydrides I from the enone-acid and 2,4,6-TCBC, followed by subsequent nucleophilic attack of the NHC catalyst, leading to acyl azolium II (Scheme 3). Subsequent deprotonation gives the corresponding azolium enolate III, with cyclisation proceeding by either a formal concerted [4+2] cycloaddition or an alternative stepwise Michael addition (5-exo-trig) followed by lactonisation (6-exo-trig). The observed product configuration is consistent with re-face addition of the enolate to the si-face of the tethered enone. This can be rationalised by the simple stereochemical model IV, consistent with the enolate adopting a (Z)-configuration and being periplanar to the triazolium ring and orthogonal to the N-mesityl group, giving the preferred cis-product V. Ring-opening of the dihydropyranone by a nucleophile (in this case morpholine) forms the desired 2,3-disubstituted 2,3-dihydrobenzofuran derivative VI.

Scheme 3. Proposed mechanism and stereochemical model.

3. Conclusions

In summary, the generation of azolium enolates from enone-acids and an NHC, and their subsequent intramolecular cyclisation with a pendant enone has been demonstrated for the preparation of heterocyclic products. Extensive investigation on a model system showed the optimal reagent to form the reactive mixed anhydride intermediate was 2,4,6-trichlorobenzoyl chloride, leading to cis-dihydrobenzofuran products with high diastereo- and enantioselectivity. The scope and limitations of this process has been probed and this method extended to the generation of 6-membered ring pyran and chromene derivatives with excellent diastereo- and enantiocontrol.

4. Experimental section

Substrates 13 – 18 and 30 were synthesised following literature procedures. General procedure: Synthesis of benzofuran derivatives

The appropriate enone-acid (0.20 mmol, 1.0 equiv) and distilled iPr₂NCl (0.22 mmol, 1.1 equiv) were stirred at rt for 20 min in anhydrous CH₂Cl₂ (3 mL) in a Schlenk flask containing 4 Å molecular sieves. Distilled 2,4,6-trichlorobenzoyl chloride (0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 2 h then cooled down to 0 ºC using an immersion cooler. NHC precatalyst 10 (0.02 mmol, 10 mol%) was added, followed with distilled iPr₂NCl (0.50 mmol, 2.5 equiv) and the reaction mixture was stirred at 0 ºC using an immersion cooler for 2 h. The appropriate nucleophile (0.30 – 2.0 mmol, 1.5 – 10 equiv) and when required DMAP (0.04 mmol, 20 mol%) were added and stirring was carried on at 0 ºC for the required amount of time. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by flash silica column chromatography to give the desired product.

HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. Authentic racemic samples were prepared using racemic chiral catalyst using the same reaction procedures.

2-(2,3,5-R)-2-(Morpholine-4-carbonyl)-2,3-dihydrobenzofuran-3-yl-1-phenylethan-1-one 12

Following the general procedure, enone-acid 9 (56 mg, 0.20 mmol), distilled iPr₂NCl (38 µL, 0.22 mmol) in anhydrous CH₂Cl₂ (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHCl precatalyst 10 (7.4 mg, 0.02 mmol, 10 mol%) then distilled iPr₂NCl (88 µL, 0.50 mmol) at 0 ºC for 24 h followed by ring-opening with morpholine (26 µL, 0.30 mmol) at 0 ºC for 4 h gave a crude brown oil (272 mg, > 95:5 dr) that was purified using Biogel® Isolera™ 4 [SNAP Ultra 10 g, 36 mL min⁻¹, CH₂Cl₂; Et₂O (95:5 CV, 95:5 to 80:20 15 CV, 80:20 10 CV)] to give the title compound (86 mg, 94%, > 95:5 dr) as a yellow oil (δ 6.45–5.5 (α, 1.03, CH₂Cl₂); Chiral HPLC OD-H (92:8 hexane : IPA, flow rate 1.00 mL·min⁻¹, 211 nm, 30 ºC) t₀ major: 74.6 min, t₀ minor: 73.1 min, 97.3% er; vax (film) cm⁻¹ 1676 (C=O ketone), 1647 (N=C=C-O amide I), 1597, 1479, 1458, 1449, 1231 (Ar–O–R), 1113 (R–O–R); 1H NMR (400 MHz, CDCl₃) δ: 3.15 (1H, dd, J = 18.4, 4.3, C(3)(CH₃)₂H), 3.22–3.34 (2H, m, (CH₂)₂); C(2)(CH₃)₂H, 3.42–3.50 (1H, m, (CH₂)₂), 3.51–3.59 (3H, m, (CH₂)₂ and (CH₂)₂), 3.65–3.78 (3H, m, C(3)(CH₂)₂ and (CH₂)₂), 4.41 (1H, td, J = 9.1, 4.3, C(3)H₃), 5.68 (1H, d, J = 8.8, C(2)H), 6.86–6.93 (2H, m, ArH × 2), 7.12–7.20 (2H, m, ArH × 2), 7.42–7.49 (2H, m, COArC(3)H₃), 7.54–7.61 (1H, m, COArC(4)H), 7.90–7.97 (2H, m, COArC(2,6)H), 13C(1H) NMR (101 MHz, CDCl₃) δ: 40.3 (C(3)), 40.7 (C(3)CH₃), 41.9 (C(3)H), 46.0 (C(2)H), 66.1 ((CH₂)₃), 66.5 ((CH₂)₃), 79.9 (C(2)), 110.0 (ArCH), 121.3 (ArCH), 124.0 (ArCH), 128.2 (COArC(2,6)), 128.78 (COArC(13,5)), 128.84 (ArCH), 129.1 (C(6a)), 131.6 (COArC(14), 136.3 (COArC(11)), 159.0 (C(7a)), 167.0 (C(2)CH), 192.8 (COP), m/z (NSI⁺) 374 ([M + Na]⁺), 315, 352 ([M + H]⁺, 100%); HRMS (NSI⁺) C₂₁H₂₀NO₃ [M⁺H]⁺ 352.1456 found 352.1543 (<0.8 ppm). Selected date for minor-trans-diastereoisomer 1H NMR (400 MHz, CDCl₃) δ: 3.37 (1H, app d, J = 8.9, C(3)(CH₂)₃), 4.56–4.62 (1H, m, C(3)H), 5.15 (1H, d, J = 5.9, C(2)H₂), 6.81 (1H, app d, J = 8.0, ArH), 7.36 (1H, app s, ArH), 7.97–7.98 (1H, m, COArCH).
Following the general procedure, enone-acid 16 (59 mg, 0.20 mmol), distilled isoprene (38 µL, 0.22 mmol) in anhydrous CH2Cl2 (3 mL) at rt for 20 min followed by distilled 2,4,6-trichlorobenzoyl chloride (34 µL, 0.22 mmol) at rt for 2 h followed by NHC precatalyst 10 (7.4 mg, 0.02 mmol, 10 mol%) then distilled isoprene (88 µL, 0.50 mmol) at 0 ºC for 4 h gave a crude yellow oil (742 mg, 95:5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mmol min⁻¹, pentane : EtOAc (100° 0 10 CV, 1000 to 50:20 CV, 50:50 CV)] to give the title compound (41 mg, 72% yield). [1]H NMR (377 MHz, CDCl3) δ: 7.12–7.23 (2H, m, ArH × 2), 7.72 (2H, d, J = 8.2, COArC(3,5)); 8.00–8.06 (2H, m, COArC(3,5)); 1.81 (9H, d, J = 4.6, CO2C(2,6)); 2.06 (6H, s, CH3(2,6)); 3.97 (3H, s, OCH3); 4.54 (1H, app q, J = 6.6, CH(2)); 6.67–6.92 (2H, m, ArH × 2), 7.13–7.20 (2H, m, ArH × 2).
Following the general procedure, enone-acid 9 (56 mg, 0.20 mmol), distilled
$p$_{2}Re(N) (38 µL, 0.22 mmol) in anhydrous CHCl$_3$ (3 mL) at rt for 20 min followed by
distilled 2,4,6-trichlorobenzyl chloride (34 µL, 0.22 mmol) at rt for 2 h
followed by NH precipitate 10 (7.4 mg, 0.02 mmol, 10 mol%) then
distilled $p$_{2}Re(N) (88 µL, 0.50 mmol) at 0°C for 24 h followed by ring-opening with
piperidine (30 µL, 0.30 mmol) at 0°C for 19 h gave a crude brown oil (276 mg, >
95.5 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL
min$^{-1}$, pentane : EtOAc (95.5 : CV, 95.5 : 80 to 20 15 CV, 80 to 20 10 CV) to
give the title compound (46 mg, 69%, 95.5 dr) as an orange oil.

(2,3,5,6-tetraisopropyl-1-methyl-2,3,3a,4,5,6,10,11,12,12a-decaphenyl-
2,3,3a,4,5,6,7,8,9,10,11,12-dodecahydro[1,8]-cyclopenta[g]-
fluorene) 22

Following the general procedure, enone-acid 9 (56 mg, 0.20 mmol), distilled
$p$_{2}Re(N) (38 µL, 0.22 mmol) in anhydrous CHCl$_3$ (3 mL) at rt for 20 min followed by
distilled 2,4,6-trichlorobenzyl chloride (34 µL, 0.22 mmol) at rt for 2 h
followed by NH precipitate 10 (7.4 mg, 0.02 mmol, 10 mol%) then
distilled $p$_{2}Re(N) (88 µL, 0.50 mmol) at 0°C for 24 h followed by ring-opening with
EtNH$_2$ (104 µL, 1.00 mmol) at 0°C for 19 h gave a crude dark orange oil (254 mg, 90-
10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL
min$^{-1}$, pentane : EtOAc (95.5 : CV, 95.5 : 80 to 20 15 CV, 80 to 20 10 CV) to
give the title compound (46 mg, 69%, 95.5 dr) as an orange oil.

Following the general procedure, enone-acid 9 (56 mg, 0.20 mmol), distilled
$p$_{2}Re(N) (38 µL, 0.22 mmol) in anhydrous CHCl$_3$ (3 mL) at rt for 20 min followed by
distilled 2,4,6-trichlorobenzyl chloride (34 µL, 0.22 mmol) at rt for 2 h
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distilled $p$_{2}Re(N) (88 µL, 0.50 mmol) at 0°C for 24 h followed by ring-opening with
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followed by NH precipitate 10 (7.4 mg, 0.02 mmol, 10 mol%) then
distilled $p$_{2}Re(N) (88 µL, 0.50 mmol) at 0°C for 24 h followed by ring-opening with
EtNH$_2$ (104 µL, 1.00 mmol) at 0°C for 19 h gave a crude dark orange oil (254 mg, 90-
10 dr) that was purified using Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL
Ultra 10 g, 36 mL min⁻¹, Hexane : EtOAc (100:5 CV, 1000 to 80:20 15 CV) to give the title compound (40 mg, 72%, >95:5 dr) as a yellow solid with data in accordance with the literature. [1] \[
\begin{align*}
&\text{1H NMR (126 MHz, CDCl₃): } \delta 29.8 (C_3), 39.7 (C_{4a}), 39.7 (C_{8a}), 65.3 (C_{8i}), 67.2 (C_{6i}), 104.0 (C_{4i}), 124.7 (C_3(C₃ArC)), 129.3 (C_3(C₃ArC)), 132.2 (C_3(C₃ArC)), 150.3 (C₃), 168.6 (C_1); \text{ m/z (ESI) } 253 \text{ [M + Na]}^{+}, 271 \text{ [M + Na + H]O}^{+}, 100%; \text{ HRMS (ESI) } \text{C}_{19}\text{H}_{20}\text{O}_{2}\text{Nan} \text{ [M + Na]} \text{ found } 253.0833 \text{ requires } 253.0841 \pm 0.58 \text{ ppm}.
\end{align*}
\]

Acknowledgments

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References and notes


Supplementary Material

For NMR spectra and HPLC traces see the Supporting Information.