# *APPENDIX 8*

## *Catalytic Asymmetric Alkylations of* Ortho-*Quinone Methides*[†]

## A8.1 INTRODUCTION

### *A8.1.1 ASYMMETRIC ALKYLATIONS OF HALO-OXINDOLES*

The enantioselective synthesis of chiral α-quaternary oxindoles and their application to total synthesis has been a long-standing goal in our research group. This project was initially inspired by our efforts toward natural product synthesis, wherein the asymmetric alkylation of a 3-halooxindole (**300**) was conceived as a method for installing one of the two vicinal quaternary centers in communesin B (**302**, Scheme A8.1.1). While a variety of other catalytic enantioselective methods for installing this motif have been developed, this transformation represented the first case in which the oxindole unit served as an electrophilic reaction partner in an enantioselective transformation.[1]

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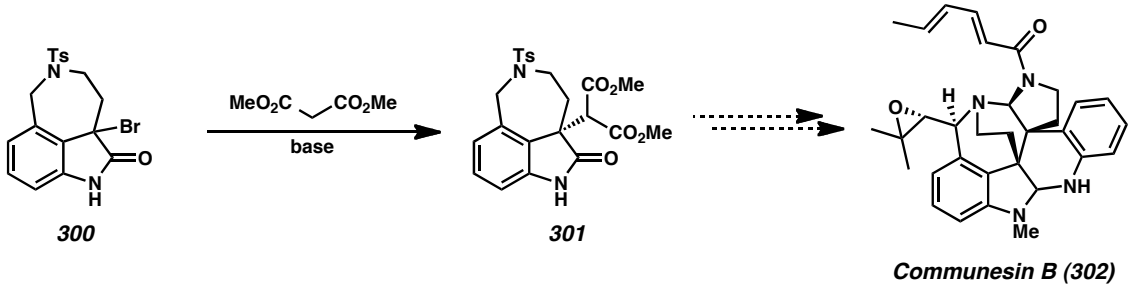
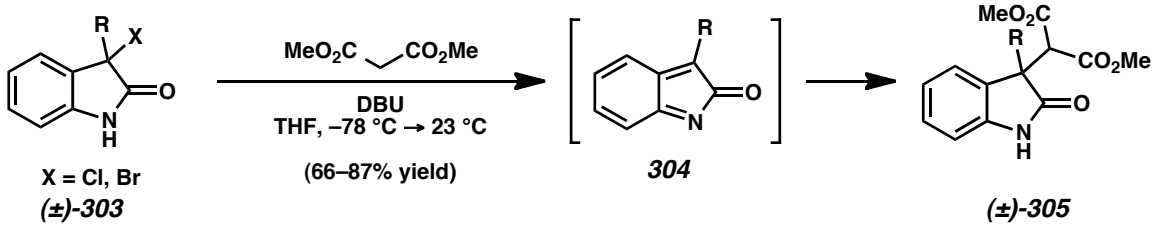
[†] This appendix was adapted from a research report produced for the author's candidacy examination. Aspects of this work are currently being investigated in collaboration with Christopher Tonge, an undergraduate researcher in the Stoltz group.

*Scheme A8.1.1. Proposed key step toward the synthesis of communesin B (**302**)*



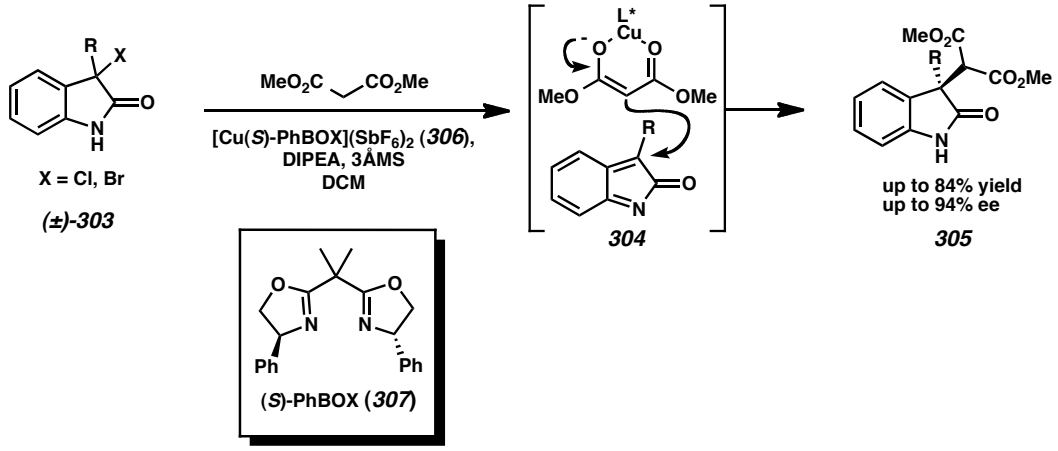

Our group reported conditions in 2007 for a non-stereoselective alkylation reaction of 3-halooxindoles, which tolerated a variety of aryl and alkyl functionality at the 3-position, proceeding via a putative *ortho*-azaxylylene intermediate (**304**, Scheme A8.1.2).[2] The model compound for communesin B (**300**, *c.f.* Scheme A8.1.2) was alkylated in 87% yield.

*Scheme A8.1.2. Discovery of the alkylation of 3-halooxindoles to form racemic products*



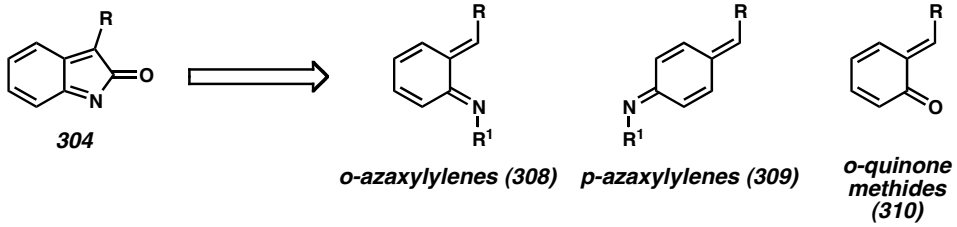

Soon afterward, the Stoltz group established conditions for an enantioselective variant of this reaction using a cationic copper (II) bisoxazoline complex (**306**).[1] With this catalytic system, quaternary stereocenters were installed in high yields and enantiomeric excesses (Scheme A8.1.3). Our group proposed that the copper catalyst binds to the malonate nucleophile, generating a chiral environment for reaction with prochiral *o*-azaxylylene **304**. This hypothesis suggests the potential for enantioselective nucleophilic additions to other prochiral, activated electrophiles.

*Scheme A8.1.3. Catalytic enantioselective stereoablative alkylation of* 3-halooxindoles




We therefore considered acyclic analogues of the original system including acyclic *ortho*-azaxylylenes (**307**),[3] *para*-azaxylylenes (**308**) and analogous *ortho*-quinone methides (**309**) (Scheme A8.1.4).

*Scheme A8.1.4. Reactive intermediates analogous to cyclic ortho-azaxylylenes* ***304***



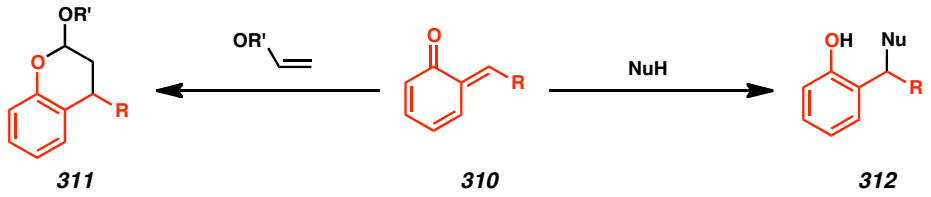

Some progress has been made toward investigating each of these compound classes within our research group.[4] Described in this report are efforts to develop a method for asymmetric alkylations of *ortho*-quinone methides (OQMs).

## *A8.1.2* ORTHO-*QUINONE METHIDES*

*Ortho*-quinone methides (OQMs, **310**) are reactive intermediates observed in both natural and synthetic systems.[5] Under ordinary circumstances, OQMs are transient species, formed in situ from a stable precursor, often by breaking aromaticity. Products

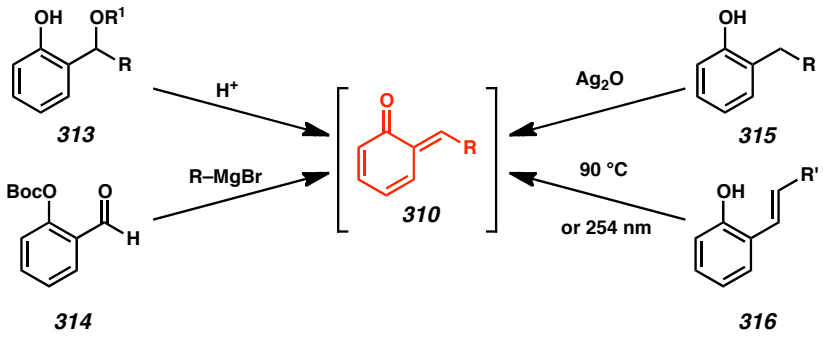
of OQMs primarily include [4+2] cycloaddition adducts (**311**) and 1,4-conjugate addition products (**312**), and their high reactivity is attributed to the rearomatization afforded through product formation (Scheme A8.1.5).

*Scheme A8.1.5. Common reactions of* ortho-*quinone methides*




OQMs can be generated from a number of precursors and under a variety of conditions. These include thermal,[6] photochemical,[7] oxidative,[8] reductive,[9] acidic[10] and basic conditions (Scheme A8.1.6). Each of these methods carries certain advantages and drawbacks related to the stability and reactivity of the precursor, susceptibility to side reactions, and compatibility with the desired reaction mode.[5] For the purposes of applying OQMs as electrophilic parters under conditions closely related to those optimized for 3-halooxindoles, a suitable precursor would be activated in the presence of base and a Lewis acid.

*Scheme A8.1.6. Common* ortho-*quinone methide (**310**) precursors*

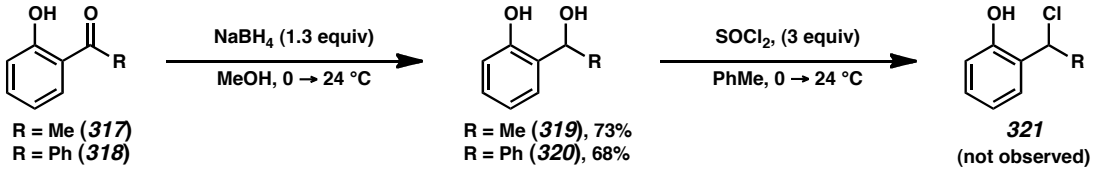


## A8.2 DEVELOPMENT OF A BASE-ACTIVATED OQM PRECURSOR

### *A8.2.1 INITIAL EFFORTS*

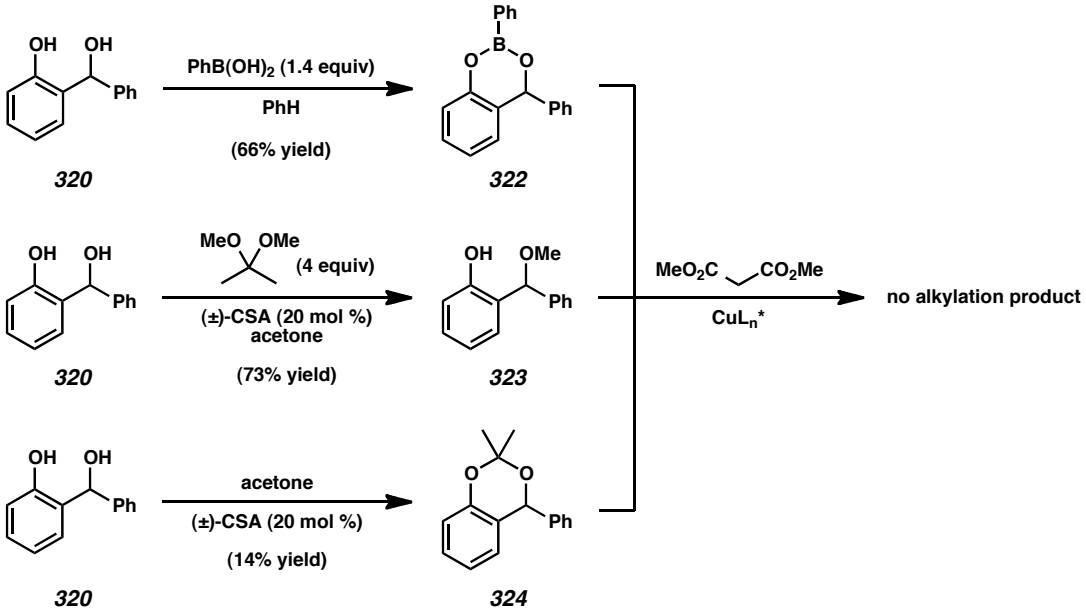
We sought to prepare *o*-hydroxybenzyl chlorides—a direct analogue of the 3-halooxindole starting materials—capable of undergoing base-promoted elimination to generate the OQM under the previously optimized alkylation conditions. Treatment of 2'-hydroxyacetophenone (**317**) and 2-hydroxybenzophenone (**318**) with sodium borohydride produced their corresponding benzyl alcohols (Scheme A8.2.1). Unfortunately, upon treatment with thionyl chloride we found that the desired materials were too unstable to be isolated.

*Scheme A8.2.1. Attempts to prepare substituted* o*-hydroxybenzyl chlorides (**321**)*



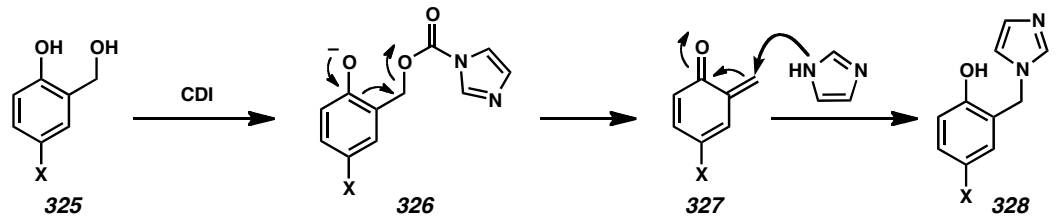

We turned instead to other known OQM precursors, dioxaborin **322**, acetonide **324**, and methoxide **323**, considering the possibility that the chiral Lewis acid used in the halooxindole alkylation system may serve to activate the precursors. Dioxaborin **322** was prepared by condensation of phenylboronic acid with diol **320** (Scheme A8.2.2). In an attempt to prepare an acetonide with the use of 2,2-dimethoxypropane, methoxide **323** was obtained as the major product instead. We were able to isolate the desired acetonide (**324**) in low yield with the use of distilled acetone in the presence of an organic Brönsted acid. Unfortunately, none of these substrates, nor diol **320**, produced any alkylation products under the optimized conditions for halooxindole alkylation.

*Scheme A8.2.2. Synthesis and examination of several OQM precursors*




Based on these experiments and our hypothesis about the mechanism of the oxindole system, we recognized the need for a base-sensitive precursor, preferably one that would be stable to isolation and long-term storage. However, these types of substrates are not well-precedented in the literature. This is best explained by the fact that a base used to prepare the precursor may proceed to trigger formation of the OQM itself. This is exemplified by Ogata and coworkers' attempt to react diol **325** with *N*,*N*'-carbonyldiimidazole (CDI).[11] Instead of an acylated product, imidazole adduct **328** is isolated, which is likely formed via an OQM mechanism (Scheme A8.2.3).[5]

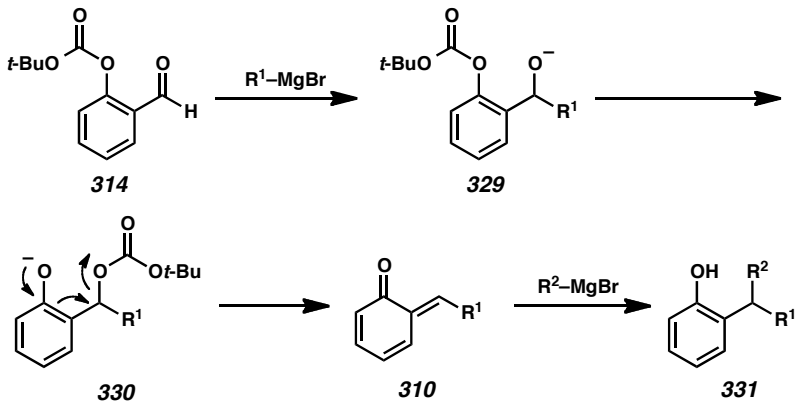
*Scheme A8.2.3. Reaction of* o-*hydroxybenzyl alcohol with carbonyldiimidazole (CDI)*



### *A8.2.2 NUCLEOPHILIC OQM GENERATION*

The Pettus group has developed a system which elegantly exploits a similar acylation-elimination sequence (Scheme A8.2.4).[12] Upon reaction with Grignard reagents, Boc-protected salicylaldehydes (**314**) undergo nucleophilic attack followed by acyl transfer and elimination to form an OQM (**310**). A second nucleophile may be added sequentially to give mixed substitution at the benzyllic position. This method bears certain disadvantages when considering the development of an asymmetric system. Firstly, the presence of additional metal salts in may lead to undesired complexity in the reaction mixture. The other limitation is that the OQM appears to be generated quantitatively prior to reaction with the second nucleophile, which could result in a significant unselective background reaction under asymmetric alkylation conditions. Conditions affording a low, steady-state concentration of reactive OQM would be preferable in asymmetric alkylation efforts.

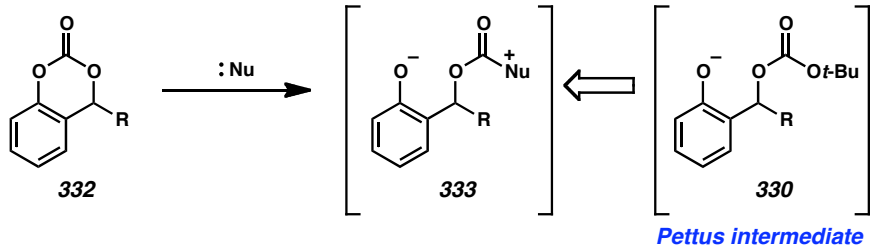
*Scheme A8.2.4. Grignard-promoted OQM generation via acyl-transfer/elimination*




We considered the cyclic carbonate **332** to be a potential candidate as a substrate for an enantioselective alkylation. Nucleophilic opening of the carbonate would afford an

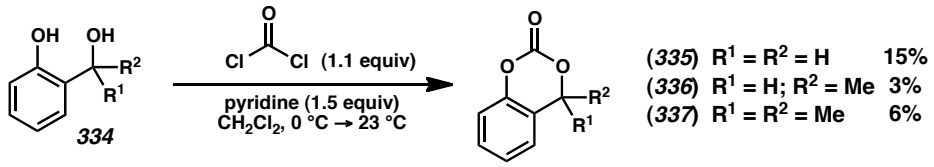
acyl benzyl alcohol derivative (**333**) which would serve as an analogue to Pettus's intermediate (**330**, Scheme A8.2.5).

*Scheme A8.2.5. Cyclic carbonates as OQM precursors*



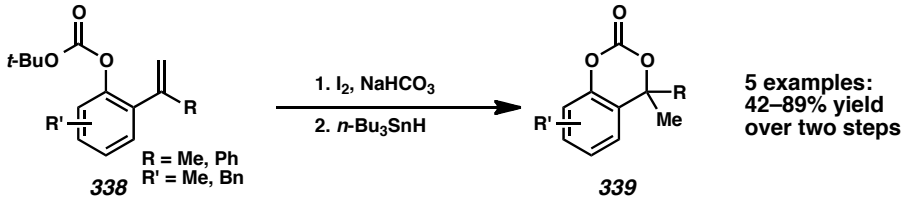

At the outset of this work, there were only two reports in the literature describing the synthesis of cyclic carbonates of this type, neither of which is in the context of *ortho*-quinone methide generation.[13] The first involves cyclization of *o*-hydroxybenzyl alcohols (**334**) with phosgene using pyridine as a base; however, the yields for this transformation were quite low, likely due to OQM generation under the reaction conditions (Scheme A8.2.6).[14]

*Scheme A8.2.6. Podraza synthesis of cyclic carbonates with phosgene*



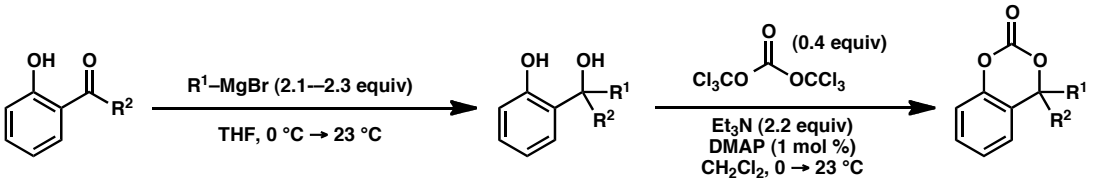

The other known method for the synthesis of these substrates involves an iodocyclization of Boc-protected *o*-hydroxystyrenes (**338**) followed by a tributyltin hydride reduction of the resulting alkyl iodide.[15] While the yields are good, this route is limited in that the *o*-hydroxystyrenes are not broadly commercially available. In addition, the reaction sequence results in the installation of a methyl group at the benzylic position which may not always be desired (Scheme A8.2.7).

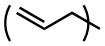
*Scheme A8.2.7. Synthesis of cyclic carbonates by iodination/cyclization sequence*




Based on its potential amenability to a broad substrate scope, we chose to employ Podraza's strategy for carbonate synthesis with several modifications. First, we used triphosgene as a safe, more easily handled surrogate for phosgene. In addition, we substituted the pyridine with the less nucleophilic base triethylamine, accompanied by catalytic DMAP. Also, the base was added slowly to the rest of the reaction mixture in order to limit the quantity of free base in solution. Overall, these modifications resulted in a marked improvement in yield in comparison to the original conditions, and a variety of substrates could be prepared in a two-step sequence from inexpensive, commercially available starting materials (Table A8.2.1). Future investigations may examine broader use of these carbonates as thermally or base initiated OQM precursors.

*Table A8.2.1. Two-step synthesis of carbonate OQM precursors*



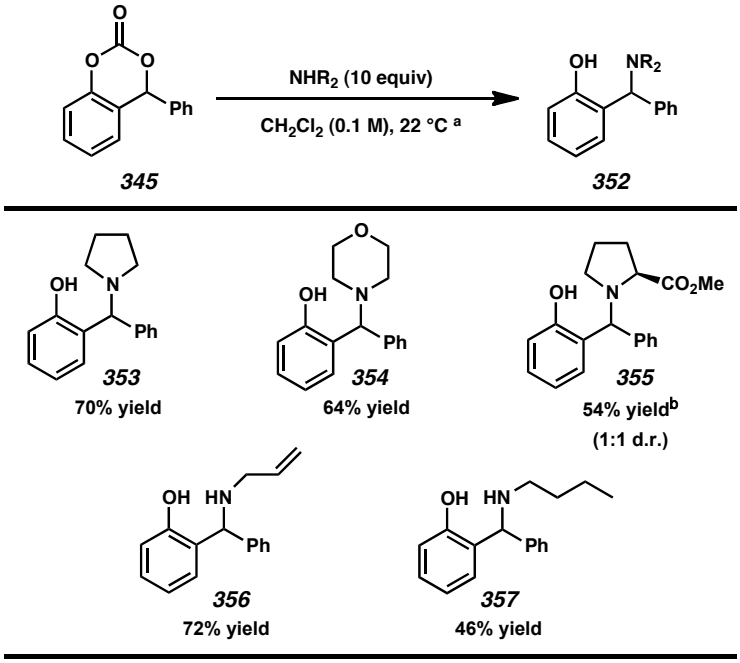

| *entry* | $R^1$ | $R^2$ | *Diol Product* | *Yield*[a] | *Carbonate* | *Yield*[a] |
|---|---|---|---|---|---|---|
| 1 | **Ph** | **H** | ***320*** | 94% | ***345*** | 79% |
| 2 | **Ph** | **Me** | ***340*** | 81% | ***346*** | 82% |
| 3 |  | **H** | ***341*** | 65%[b] | ***347*** | 40% |
| 4 |  | **H** | ***342*** | 92% | ***348*** | 69% |
| 5 |  | **H** | ***343*** | 52%[b] | ***349*** | 43% |
| 6 |  | **H** | ***344*** | 70%[c] | ***350*** | 89% |
| 7 | **Me** | **H** | ***319*** | –[d] | ***351*** | 77% |

[a] Isolated yields [b] Reaction performed in $Et_2O$ [c] This product was prepared by deprotonation of 1-hexyne with *n*-BuLi [d] This product was prepared by $NaBH_4$ reduction of 2'-hydroxyacetophenone

## A8.3 REACTIVITY WITH *N*- AND *O*-BASED NUCLEOPHILES

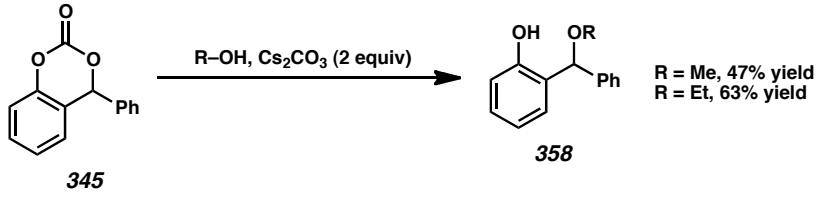
With a general and operationally simple route in hand to cyclic carbonates (e.g. **345**), we studied their reactivity under mild conditions, with amine and alcohol nucleophiles. We found that benzylic secondary and tertiary amines could be prepared in moderate yields by treatment of carbonate **345** with an excess of amine (Table A8.3.1). Alternatively, benzylic ethers were formed with similar efficiency by reaction of the same carbonate (**345**) in an alcoholic solvent in the presence of base (Scheme A8.3.1).

*Table A8.3.1 Reaction of carbonate **345** with amine nucleophiles*




[a] Isolated yields. [b] Proline methyl ester • HCl and exogenous base were used.

*Scheme A8.3.1. Reaction of carbonate **345** with alcohols*

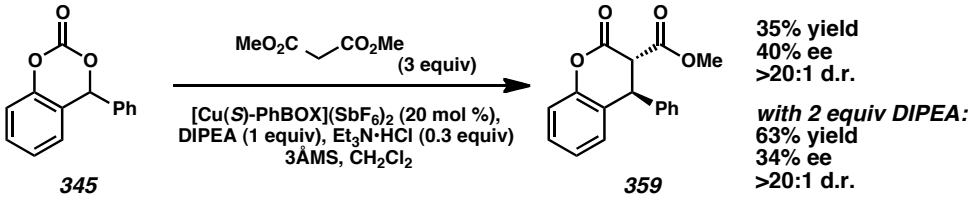



## A8.4 ASYMMETRIC ALKYLATION WITH MALONATES

### *A8.4.1 INITIAL DISCOVERY*

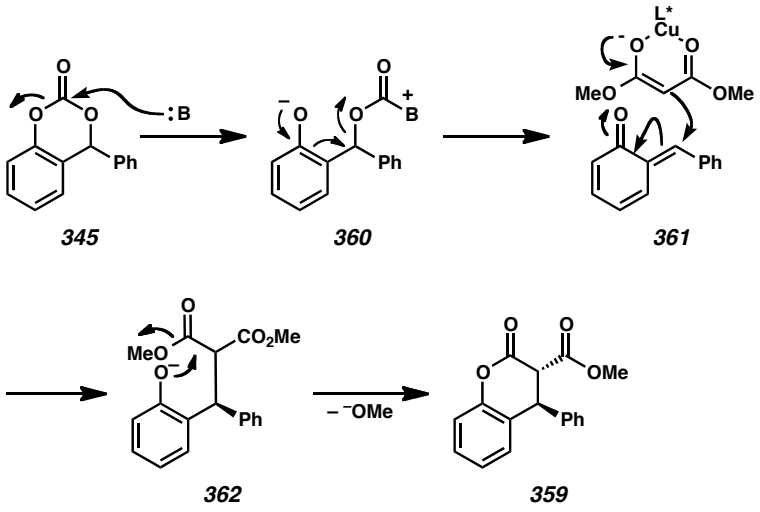
We turned our attention to the development of an enantioselective, stereoablative alkylation reaction. On our first attempt, using the halooxindole alkylation conditions,[16] we were delighted to observe conversion of cyclic carbonate **345** to dihydrocoumarin **359** with modest enantioselectivity (Scheme A8.4.1).

*Scheme A8.4.1. Initial observation of asymmetric alkylation with dimethylmalonate*



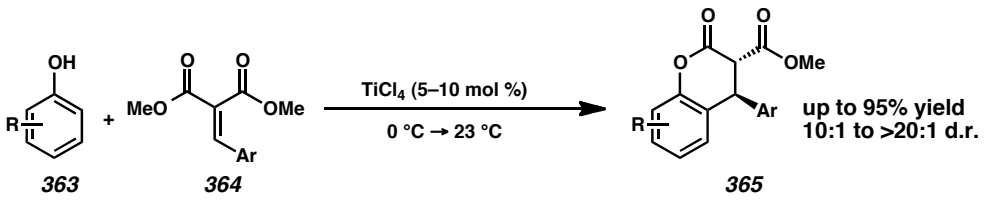

Under these conditions, a base-promoted decarboxylation of carbonate **345** occurs, forming the OQM (**361**, Scheme A8.4.2).[17] An enantioselective alkylation and lactonization ensue to form dihydrocoumarin **359**.

*Scheme A8.4.2. Proposed mechanism for OQM alkylation reaction*




The diastereoselectivity observed in our initial result is similar to that seen in racemic syntheses of similar dihydrocoumarins. For instance, Tunge and co-workers reported a racemic Lewis acid coupling of phenols (**363**) with benzylidene malonate esters (**364**) to produce similar products (**365**) with high diastereoselectivites (Scheme A8.4.3).[18] Although thermodynamic equilibration of the product is possible, it remained unclear at this point whether the high diastereomeric ratio in our system is a result of equilibration or an irreversible diastereoselective cyclization.

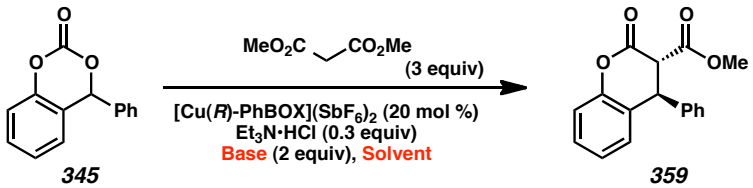
*Scheme A8.4.3. Tunge's Lewis acid catalyzed coupling of phenols and benzylidene malonates*




## A8.4.2 REACTION OPTIMIZATION

Following our initial enantioselective alkylation result, we sought to optimize the reaction for ee and yield. We initially examined eight solvent systems as well as four different bases with the assistance of a Symyx robot module (Table A8.4.1). We found that triethylamine and diisopropylethylamine generally gave comparable ee's, while DBU gave little product formation and negligible enantioselectivity. With cesium carbonate, the enantioselectivity was improved considerably; in the best case, with the use of 1,2-dichloroethane (DCE) as a solvent, 78% ee was achieved. In this case, the use of a heterogeneous base potentially limits the amount of base (and by extension, OQM intermediate) in solution as the reaction progresses.

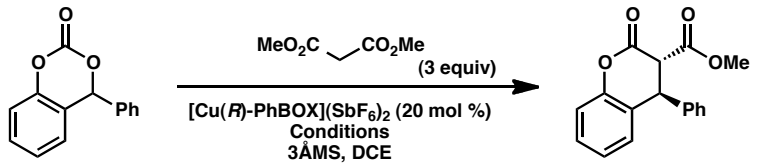
*Table A8.4.1. Solvent and base screen for OQM alkylation reaction*




| (% ee) | $CH_2Cl_2$ | DCE | $CH_2Cl_2$/PhMe (1:1) | PhMe | $CH_2Cl_2/Et_2O$ (1:1) | $CH_2Cl_2$/THF (1:1) | THF | *t*-BuOH |
|---|---|---|---|---|---|---|---|---|
| $Et_3N$ | 37 | 51 | 35 | 40 | 35 | 44 | 27 | 53 |
| DIPEA | 36 | 54 | 33 | 27 | 33 | 37 | 29 | 54 |
| DBU | 0 | 0 | 0 | 9 | – | 0 | 0 | – |
| $Cs_2CO_3$ | 63 | 78 | 61 | 57 | 69 | 36 | 48 | 15 |

However, when attempts were made to replicate the best result by hand, we were unable to reproduce the 78% e.e. obtained with the Symyx robot. Indeed, after several attempts were made, the enantiomeric excesses were approximately 52% and the dihydrocoumarin product (**359**) was obtained in 55% yield at most (Scheme A8.4.4).

*Scheme A8.4.4. Reproduction attempts for Symyx optimized conditions*




***345*** ***359***

***Conditions:***

**$Et_3N$ (0.3 equiv), $Cs_2CO_3$ (2 equiv): 55% yield, 52% ee**
**$Et_3N$·HCl (0.3 equiv) $Cs_2CO_3$ (2 equiv): 48% yield, 52% ee**
**$Et_3N$ (0.3 equiv): 40% yield, 55% ee**

Undeterred, we continued to screen conditions and examined the use of other metal salts and ligands in this reaction (Figure 8.4.1). For the purpose of higher throughput screening, catalyst complexes were formed in situ from copper (II) triflate and ligand, which gave comparable results to the preformed hexafluoroantimonate complex (Table A8.4.2). We examined other aryl (entries 4–6) and alkyl (entries 7–9) bisoxazoline ligands as well as other ligand classes (entries 10–12), and obtained our best result with perfluorinated phenyl bisoxazoline ligand (**368**) (entry 6).[19] Once again however, we were unable to reproduce this result, obtaining the dihydrocoumarin product (**359**) in lower ee's in replicate reactions (entries 13 & 14).

*Figure 8.4.1. Ligands examined in the* o-*QM asymmetric alkylation screen*

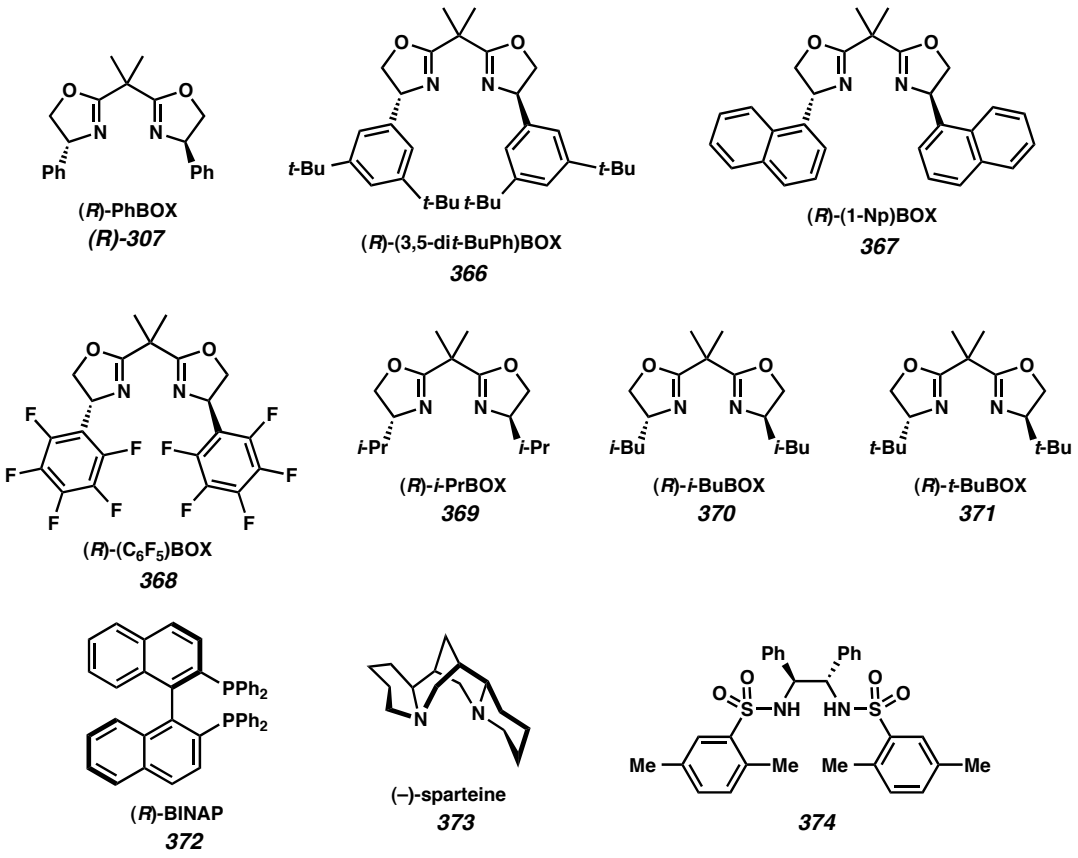
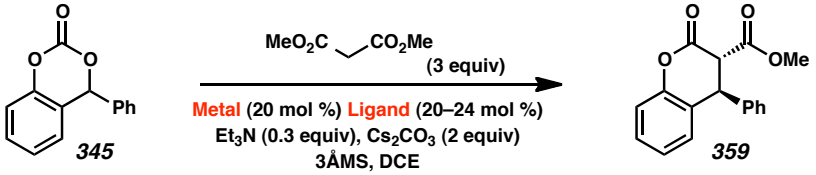



*Table A8.4.2. Catalyst screening for OQM alkylation reaction*



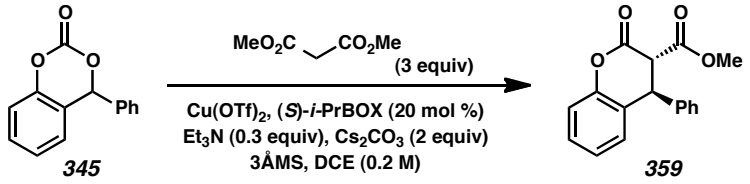

| *Entry* | *Metal* | *Ligand* | *ee (%)* | *Entry* | *Metal* | *Ligand* | *ee (%)*[a] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | (*R*)-PhBOX (***307***) | 52 | 8 | $Cu(OTf)_2$ | (*R*)-*i*-BuBOX (***370***) | 49 |
| 2 | $Zn(OTf)_2$ | (*R*)-PhBOX (***307***) | 58 | 9 | $Cu(OTf)_2$ | (*R*)-*t*-BuBOX (***371***) | 61 |
| 3 | $Ln(OTf)_3$ | (*R*)-PhBOX (***307***) | 57 | 10 | $Cu(OTf)_2$ | (*R*)-BINAP (***372***) | 17 (40%) |
| 4 | $Cu(OTf)_2$ | (*R*)-(3,5-di*t*-BuPh)BOX (***366***) | –28 | 11 | $Cu(OTf)_2$ | (–)-sparteine (***373***) | -30 (5%) |
| 5 | $Cu(OTf)_2$ | (*R*)-(1-Np)BOX (***367***) | 60 | 12 | $Cu(OTf)_2$ | **374** | 0 (33%) |
| 6 | $Cu(OTf)_2$ | (*R*)-($C_6F_5$)BOX (***368***) | –74 | 13 | $Cu(OTf)_2$ | (*R*)-($C_6F_5$)BOX (***368***) | 56 (44%) |
| 7 | $Cu(OTf)_2$ | (*R*)-*i*-PrBOX (***369***) | 61 | 14 | $Cu(OTf)_2$ | (*R*)-($C_6F_5$)BOX (***369***) | 53 (48%)[b] |

[a] Isolated yields (%) in parentheses. [b] Reaction run with 10 mol% catalyst loading.

We were interested in learning more about the reaction in order to gain insight into the irreproducibility of the process. Accordingly, we altered various components of the reaction mixture, using *i*-PrBOX (**369**) due to the limited availability of the $(C_6F_5)$BOX ligand (**368**, Table A8.4.3). While changing the quantity of triethylamine had little effect, lowering the amount of cesium carbonate improved the yield (entry 4). Adjusting the equivalents of malonate dropped the yield slightly (entries 6, 7), and lowering the reaction concentration slightly improved the yield at the expense of enantiomeric excess (entry 8).

We considered the possibility that the methoxide produced from the product cyclization may be lowering the enantioselectivity by binding to the catalyst; substituting either the triethylamine or cesium carbonate for sodium methoxide had a deleterious effect on the yield and enantiomeric excess (entries 9, 10). Furthermore, the substitution of 3Å molecular sieves for 4Å sieves improved the enantioselectivity albeit at the expense of yield.

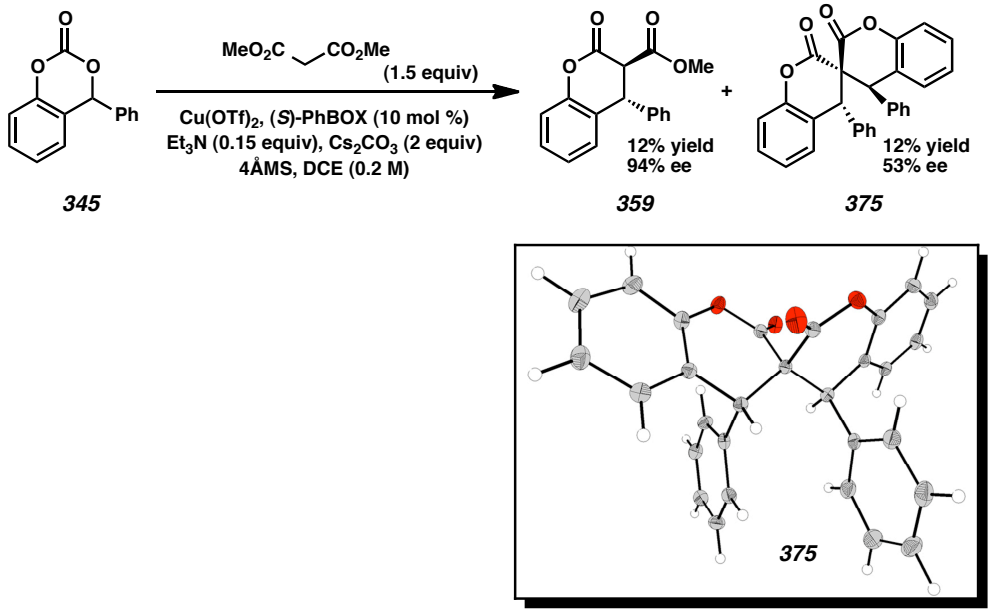
*Table A8.4.3. Modifications to OQM alkylation conditions*



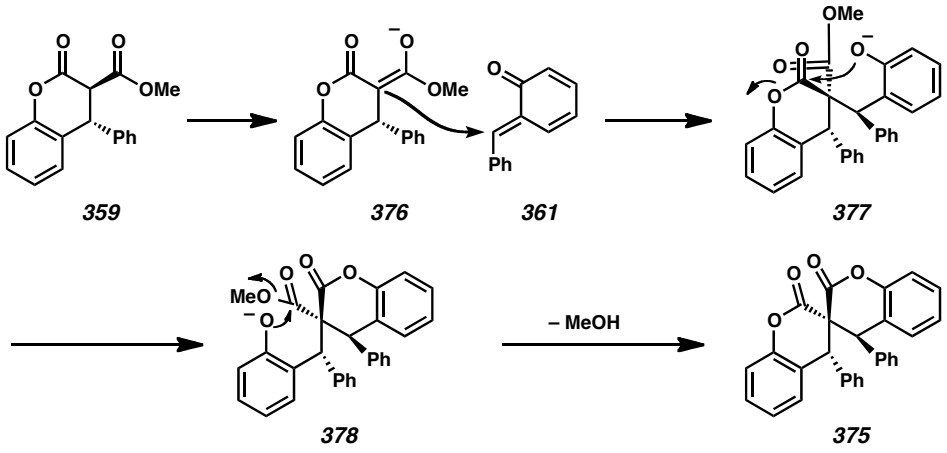

| *Entry* | *Modifications* | *yield (%)* | *ee (%)* |
|---|---|---|---|
| 1 | none | 48 | 62 |
| 2 | $Et_3N$ (0.15 equiv), $Cs_2CO_3$ (2 equiv) | 41 | 58 |
| 3 | $Et_3N$ (0.6 equiv), $Cs_2CO_3$ (2 equiv) | 50 | 60 |
| 4 | $Et_3N$ (0.3 equiv), $Cs_2CO_3$ (1 equiv) | 66 | 61 |
| 5 | DIPEA (0.3 equiv), $Cs_2CO_3$ (2 equiv) | 42 | 58 |
| 6 | $MeO_2C$ $CO_2Me$ (2 equiv) | 38 | 58 |
| 7 | $MeO_2C$ $CO_2Me$ (4 equiv) | 40 | 57 |
| 8 | DCE (0.1 M) | 54 | 55 |
| 9 | NaOMe (0.3 equiv), $Cs_2CO_3$ (2 equiv) | 42 | 51 |
| 10 | $Et_3N$ (0.3 equiv), NaOMe (2 equiv) | 38 | 12 |
| 11 | MS 4Å | 41 | 75 |

In an experiment where the quantities of starting material and cesium carbonate were doubled, we were surprised to obtain the dihydrocoumarin product (**359**) in a remarkably high enantiomeric excess and unusually low yield (Scheme A8.4.5). Concurrently, we were able to identify the major side product of these reactions as spirocycle **375**, which is formed from an addition of the product into a second equivalent of OQM **361**. The relative stereochemistry, confirmed by x-ray crystallography, appears counter-intuitive. Based on the orientation of the quaternary stereocenter, it appears to suggest an alkylation of enolate **376** on its more hindered face (Scheme A8.4.6). However, one may consider a mechanism which involving enolate alkylation on the less hindered face followed by inversion of the quaternary center by translactonization.

*Scheme A8.4.5. Isolation of spirocyclic bis-OQM adduct*



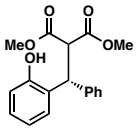
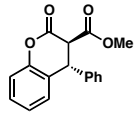

*Scheme A8.4.6. Proposed mechanism for formation of spirocycle* ***375***




With this dimerization pathway in mind, we considered the possibility that the product may be undergoing a kinetic resolution, which could account for the irreproducibility of ee in some experiments. Indeed, we found that the enantiomeric excess of the dihydrocoumarin product **359** increased over the course of the reaction (Table A8.4.4). In addition, the initial malonate adduct **379** was formed in approximately 30% ee, which effectively represents the enantioselectivity of the desired alkylation

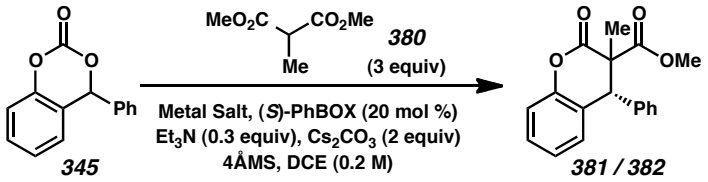
reaction. Accordingly, spirocycle **375** (*cf.* Scheme A8.4.5) is enantioenriched with respect to the first alkylation ee, consistent with the bisalkylation playing a role in a kinetic resolution. For a full picture, it will be necessary to monitor enantioenrichment of spirocycle **375** over the course of the reaction.

*Table A8.4.4. Change in enantiomeric excess of intermediate **379** and product **359** over time.*

| time (min): | | 70 | 130 | 195 | 270 | 390 |
|---|---|---|---|---|---|---|
| ***379***  | ee: | 30% | 28% | – | – | – |
| ***359***  | ee: | 26% | 30% | 51% | 62% | 68% |

In order to prevent a second alkylation event from occurring, we continued our optimization with dimethyl methylmalonate (**380**), (Table A8.4.5). An additional challenge of diastereoselectivity was introduced since the diastereomers can no longer be interconverted simply by enolization. Indeed this was reflected in our first result when we subjected malonate **380** to our best conditions. Under these conditions, it was found that the diastereomeric ratio was reduced to 2:1, and curiously, the diastereoselectivity was improved to > 20:1 when no ligand was used. When zinc triflate was substituted for copper in the presence of PhBOX, the diastereomeric ratio remained at 20:1 with comparable enantioselectivity. Notably, the diastereoselectivity was inverted with the use of metal chlorides such as zinc and cobalt (II) chloride. In addition, the use of cobalt salts reversed the enantioselectivity, perhaps a result of a tetrahedral geometry at the metal center.

*Table A8.4.5. Metal screen with dimethyl methylmalonate (**380**)*



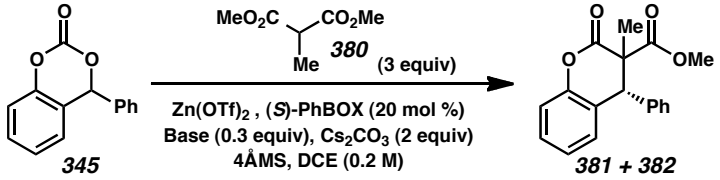

345 381 / 382

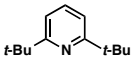
| Entry | Metal | d.r. (**381**:**382**) | ee (**381**) | ee (**382**) |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 2:1 | 35% | 72% |
| 2 | $Cu(OTf)_2$[a] | > 20:1 | – | – |
| 3 | $Zn(OTf)_2$ | > 20:1 | 30% | n.d. |
| 4 | $ZnCl_2$ | 1:4 | 64% | 52% |
| 5 | $CoCl_2$ | 1:2.1 | 4% | -31% |
| 6 | $CoCl_2$[b] | 1:1.9 | -13% | -43% |
| 7 | $CoBr_2$ | 1:1.4 | -2% | -28% |

[a] no ligand used. [b] 2 equiv ligand used.

Having discovered that zinc triflate provides excellent diastereoselectivity without compromising enantioselectivity to a large degree, we continued to optimize the reaction conditions, examining a range of amine bases and temperatures (Table A8.4.6). We have found that reducing the temperature to 10 °C boosts enantioselectivity at the expense of diastereoselectivity (entry 7). However, diastereoselectivity can be restored with judicious choice of base; for example, the use of 2,6-di-*t*-butyl pyridine gave the highest diastereomeric ratio at 10 °C, in addition to a high yield (entry 13). The highest enantioselectivity in this system to date was achieved with dimethylcyclohexyl amine (entry 8), and the best yield with triisobutylamine (entry 10).

*Table A8.4.6. Base and temperature optimization for OQM alkylation with malonate* ***380***




| *Entry* | *Base* | *Yield*[a] | *d.r.* | *ee (**381**) (%)* | *ee (**382**) (%)* |
|---|---|---|---|---|---|
| 1 | $Et_3N$ | 44% | > 20:1 | 30 | – |
| 2 | DIPEA | 54% | > 20:1 | 19 | – |
| 3 | DBU | 20% | > 20:1 | 5 | – |
| 4 |  | 45% | > 20:1 | 24 | – |
| 5 | DABCO | 60% | > 20:1 | 49 | – |
| 6 | DABCO | 4%[b] | 1:1.2 | 70 | – |
| 7 | DABCO | 77%[c] | 1:1.5 | 66 | 54 |
| 8 | $Me_2CyN$ | 60%[c] | 1:1.9 | 71 | 55 |
| 9 | $MeCy_2N$ | 57%[c] | 1:2.1 | 69 | 56 |
| 10 | $(i\text{-Bu})_3N$ | 94%[c] | 2.5:1 | 61 | 57 |
| 11 |  | 75%[c] | 1:1.3 | 70 | 52 |
| 12 | pyridine | 48%[c] | 1.4:1 | 15 | -19 |
| 13 |  | 85%[c] | 10:1 | 60 | – |

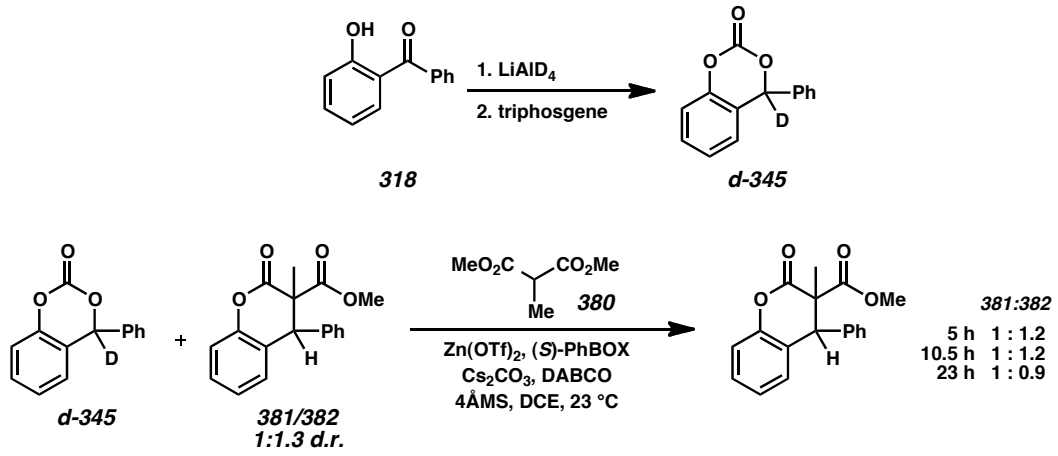
[a] Isolated yields. [b] Reaction run at 0 °C. [c] Reaction run at 10 °C

## *A8.4.3 DISCUSSION OF MECHANISM*

The relative stereochemistry of each of the diastereomers (**381** and **382**) has not been conclusively determined to date.[20] Nevertheless, the observed trends in diastereoselectivity present a mechanistic challenge for which several scenarios are possible. First, reversibility of lactonization may be considered. In such a case, the diastereoselectivity may be an issue of kinetic versus thermodynamic product formation. To test for reversible lactonization, we prepared a deuterated starting material (**d-345**), and subjected it to alkylation conditions (similar to entry 5, Table A8.4.6), spiking the

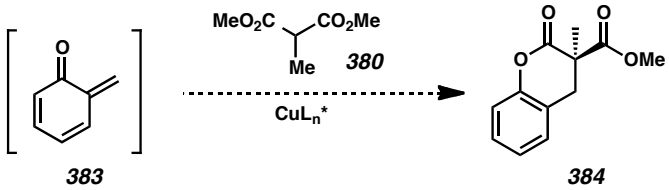
reaction with a non-deuterated mixture of diastereomeric products (Scheme A8.4.7). Since the diastereomeric ratio of the product mixture is determined based on the integration of $^1$H NMR resonances for the benzylic proton of **381/382**, products (**d-381/d-382**) formed from the deuterated starting material will not affect the observed diastereomeric ratio of the nondeuterated product (**359**). In this experiment, NMR would reveal if the diastereomers of the product are interconverting under the reaction conditions. In the event, it was found that the diastereomeric ratio did not change substantially over the course of the reaction. This result suggested that the diastereomeric products (**381** and **382**) do not interconvert on the time scale of this reaction.[21]

*Scheme A8.4.7. Deuterium labeling study: test for reversible lactonization.*




Another potential mechanistic explanation for the observed diastereoselectivity would involve a catalyst-controlled ring-closure, which could be substantiated by observing enantioselectivity in the reaction of malonate **380** with an unsubstituted OQM (**383,** Scheme A8.4.8).

*Scheme A8.4.8. Proposed test for catalyst-controlled lactonization*

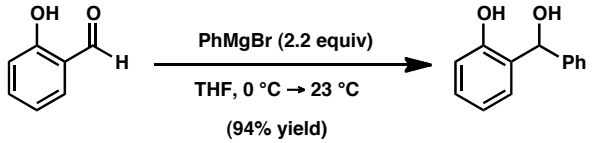



## A8.5 CONCLUSION

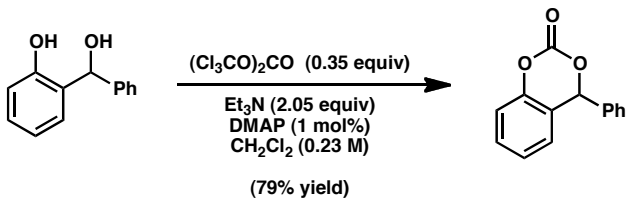
Future work will be directed toward optimizing the alkylation reaction and examining the substrate scope of the reaction. Reaction components including ligands, solvent, reagent concentration, and malonates (or β-ketoesters) must be further evaluated. In addition, further mechanistic studies will be conducted to determine factors contributing to diastereoselectivity. The scope of this reaction will be explored with the use of a variety of substituted OQMs. Finally, the cyclic carbonate precursors will be examined for their utility in other known OQM reactions.

## A8.6 EXPERIMENTAL SECTION

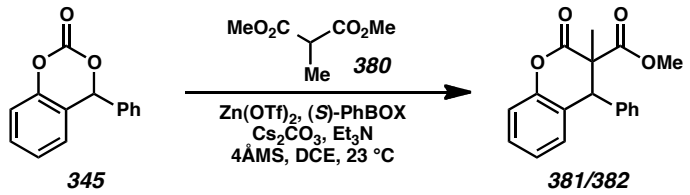
### *A8.6.1 PREPARATIVE PROCEDURES*




**Diol 320.** Representative procedure. A round-bottom flask was equipped with a magnetic stir bar, sealed with a rubber septum, flame-dried under vacuum and cooled under an inert atmosphere. To the flask was added salicylaldehyde (1.0 mL, 9.4 mmol, 1 equiv) by syringe, followed by tetrahydrofuran (50 mL). Stirring was initiated and the flask was cooled in an ice-water bath. Phenylmagnesium bromide (3.0 M in diethyl ether, 6.6 mL, 20 mmol) was added dropwise. Through the addition, the reaction mixture became dark green then grey. After 45 min, the reaction was quenched by addition of saturated ammonium chloride, and diluted with water. The bulk of the THF was removed in vacuo, and the resulting mixture was extracted with ethyl acetate (3 x 65 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on $SiO_2$ (10:1 hexanes:EtOAc) to afford diol **320** (1.76 g, 94% yield): 1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.46–7.30 (m, 5H), 7.24–7.15 (m, 1H), 6.95–6.77 (m, 3H), 6.04 (d, J = 3.2 Hz, 1H), 2.82 (d, J = 3.3 Hz, 1H).



**Carbonate 345.** To a flame-dried round-bottom flask was added diol (731.3 mg, 3.65 mmol, 1 equiv), 4-(*N*,*N*-dimethylamino)pyridine (3.2 mg, 0.026 mmol, 0.01 equiv), and triphosgene (387.7 mg, 1.28 mmol, 0.35 equiv). The flask was sealed with a rubber septum under an inert atmosphere, dichloromethane (16 mL, 0.23M) was added, stirring was initiated, and upon dissolution of the solids, the flask was lowered into an ice-water bath. To the cooled solution was added dropwise freshly distilled triethylamine (1.04 mL, 7.49 mmol, 2.05 equiv). Upon consumption of starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride and diluted with water. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organics were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on $SiO_2$ (9:9:2 toluene:hexanes:EtOAc) to afford carbonate **345** (650 mg, 79% yield): 1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.39 (m, 4H), 7.37–7.31 (m, 2H), 7.21–7.14 (m, 2H), 6.96–6.90 (m, 1H), 6.46 (s, 1H).




**Dihydrocoumarins 381/382.** Representative procedure: In a nitrogen filled glovebox, an oven-dried 1 dram vial was charged with zinc triflate (7.0 mg, 0.02 mmol, 0.2 equiv), and 4Å molecular sieves (36.8 mg). The vial was sealed with a cap lined with a teflon septum, removed from the glovebox, and placed under an inert atmosphere. To this vial was added (*S*)-PhBOX (8.3 mg, 0.025 mmol, 0.2 equiv) via syringe in freshly-

distilled 1,2-dichloroethane (DCE, 0.25 mL). Methyl dimethylmalonate (0.031 mL, 0.3 mmol, 3 equiv) was added neat via syringe, followed by carbonate **345** (22.4 mg, 0.1 mmol, 1 equiv) in DCE (0.25 mL). The reaction mixture was cooled in a 10 °C bath (dioxane) and neat triisobutylamine (0.007 mL, 0.03 mmol, 0.3 equiv) was added. Finally, under a stream of argon, solid cesium carbonate (63.9 mg, 0.2 mmol, 2 equiv) was added quickly and the vial was resealed. Upon completion, the mixture was filtered through a short plug of silica gel, then purified by column chromatography on $SiO_2$ (15:1 hexanes:EtOAc) to afford dihydrocoumarin (27.7 mg, 94% yield) as a 5:2 mixture of diastereomers **381** (61% ee) and **382** (57% ee): 1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.04 (m, 9H), 4.54 (s, 1H, **381**), 4.22 (s, 1H, **382**), 3.61 (s, 3H, **381**), 3.42 (s, 3H, **382**), 1.58 (s, 3H, **381**), 1.36 (s, 3H, **382**).

## A8.7 NOTES AND REFERENCES

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(15) Kobayashi, K.; Nakamura, D.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 489–491.

(16) A small triethylammonium impurity from the previous reaction was present in our initial experiments

(17) Exposure of the carbonate to basic conditions results in an immediate color change.

(18) Duan, S.; Jana, R.; Tunge, J. A. *J. Org. Chem*. **2009**, *74*, 4612–4614.

(19) A reversal in enantioselectivity was also observed with this ligand in the alkylation of 3-halooxindoles. Han, X. Q.; *Unpublished Results*. **2007**.

(20) NOE experiments have been conducted, with attempts to correlate the benzylic proton with the methyl group, however, the results were inconclusive; A-values for $CH_3$ and $CO_2Me$ are 1.74 and 1.2 kcal/mol respectively. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, Wiley & Sonds: New York, 1994; pp 696–697.

(21) An alternative explanation is the diastereomeric mixture used in this experiment constituted the thermodynamic product mixture. Subjection of a single diastereomer of the product to the same experiment would test this hypothesis.