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**DEVELOPMENT OF ENANTIOSELECTIVE INTRAMOLECULAR N-
ARYLATION REACTIONS FOR THE DESYMMETRIZATION OF ACHIRAL
DINITROGEN MALONAMIDE DERIVATIVES**

by

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Ryerson University, Toronto, Canada, 2006

A thesis presented to Ryerson University
in partial fulfillment of the requirements for the degree of
Master of Applied Science in the program of
Molecular Science

Toronto, Ontario, Canada, 2008

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Abstract

Development of Enantioselective Intramolecular N-Arylation Reactions for the Desymmetrization of Achiral Dinitrogen Malonamide Derivatives

by Lukasz Porosa

Molecular Science

Masters of Science 2008, Ryerson University

An effective methodology for the enantioselective intramolecular (Buchwald-Hartwig) amidation of prochiral dinitrogen malonamide derivatives has been developed in quantitative yield and good enantioselectivities. The best result was obtained based on an enantiopure (*R*)-MOP/Pd(OAc)₂ catalyst system with either Cs₂CO₃ or K₃PO₄ in refluxing THF affording the 4-methoxybenzyl substituted diamide derivative, 3-methyl-*N*,1-bis(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide, in 99% yield and 75% enantiomeric excess. This example serves as a preliminary example of a desymmetrization of prochiral dinitrogen nucleophiles by preferential N-arylation. The intermolecular version of this reaction proved to be more challenging than its intramolecular counterpart and no coupling products were obtained. Other malonamide derivatives were prepared with a pendant bromovinyl substituent at the α position and cyclized intramolecularly employing a mild Goldberg reaction to form 5-membered rings in good yield and unknown enantioselectivity.

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Table of Contents

Author's Declaration.....	ii
Abstract.....	iii
Acknowledgements.....	iv
List of Figures.....	vii
List of Schemes.....	ix
List of Tables.....	xi
List of Abbreviations.....	xii
1 INTRODUCTION.....	Error! Bookmark not defined.
1.1 Asymmetric Synthesis:.....	1
1.1.1 Enantioselective Catalysis.....	2
1.2 Carbon-Nitrogen Cross-Coupling Reactions.....	7
1.2.1 Palladium Catalyzed Buchwald-Hartwig Couplings:.....	8
1.2.2 Intramolecular Arylation of Amines and Amides.....	10
1.2.2.1 Intramolecular Arylation of Amines.....	10
1.2.2.2 Intramolecular Arylation of Amides.....	11
1.2.3 Copper Catalyzed Ullmann and Goldberg C-N Couplings:.....	16
1.2.3.1 Intramolecular Arylation of Amines with Copper.....	17
1.2.3.2 Intramolecular Arylation of Amides with Copper.....	18
1.2.4 Other developments.....	20
1.2.4.1 Heteroatom-Aryl Coupling.....	20
1.3 Enantioselective Cross-Coupling of Nitrogen Nucleophiles:.....	21
1.3.1 Chiral Amine couplings:.....	21
1.3.2 Enantioselective N-Arylations.....	23
1.3.3 Enantioselective N-Allylation.....	26
1.3.4 Enantioselective Hydroamination.....	29
1.3.5 Enzymatic Desymmetrization of α,α -Disubstituted Malonamides.....	29
1.4 Applications.....	30

2 RESULTS AND DISCUSSION.....	33
2.1 Synthesis of Malonamide Precursors.....	33
2.2 Intramolecular Aryl Amidation of 2-(2-Bromobenzyl)malonamides.....	35
2.3 Intramolecular Vinyl Amidation of Bromovinyl Malonamides:.....	46
2.4 Intermolecular Aryl Amidation.....	47
3 EXPERIMENTAL.....	50
3.1 General Considerations:.....	50
3.2 Preparation of Malonamide Derivatives.....	50
Method 3.2.1 General Procedure for Malonate Ester Alkylations.....	50
Method 3.2.2 General Procedure for the Preparation of Diacids via Ester Hydrolysis.....	55
Method 3.2.3 General Procedure for Malonamide Preparation.....	58
3.3 General Procedure for Malonamide Reduction.....	66
Method 3.3.1.....	66
3.4 General Procedure for Intramolecular Malonamide Cyclization:.....	67
Method 3.4.1 Sealed Tube:.....	67
Method 3.4.2 Under Reflux with Palladium.....	68
Method 3.4.3 Under Reflux with Copper:.....	68
4 CONCLUSION.....	76
5 REFERENCES.....	77
6 APPENDIX: NMR spectra (^1H, ^{13}C) and HPLC chromatograms.....	85

List of Figures:

Figure 1. Types of Natural and Synthetic Chiral Compounds.....	1
Figure 2. Privileged Enantioselective Ligands.....	3
Figure 3. Side view of (3 – SEGPPOS) showing the steric environment created by axially chiral bisphosphines.....	5
Figure 4. Symmetry Breaking of Achiral or <i>Meso</i> Compounds.....	6
Figure 5. The Course of an Asymmetric Reaction.....	6
Figure 6. Examples of Biologically Active Compounds Synthesized via the Buchwald-Hartwig Reaction.....	7
Figure 7. Ligands used in Pd-Catalyzed N-Arylations.....	9
Figure 8. Structures of Ligands for Milder Ullmann/Goldberg C-N Couplings....	17
Figure 9. Potential Bonds Formed with the Tandem Intramolecular Vinyl Amidation.....	19
Figure 10. Buchwald's Biaryl Ligand Family.....	20
Figure 11. Inversion of Configuration at the Nitrogen Centre.....	21
Figure 12. Structures of Chiral Phosphines utilized in the Ligand Screen.....	37
Figure 13. Inseparable Diastereomers of Naphthyl Substituted Quinolinone.....	42

Figure 14. Simplified Catalytic Cycle in a Pd Asymmetric Intramolecular Amidation Reaction of a Malonamide Derivative.....	44
---	----

Figure 15. Proposed Diastereomeric Intermediates, with Monodentate (R)-MOP as Ligand.....	44
--	----

Figure 16. Tuning of steric or electronic properties of MOP Ligands.	45
--	----

Figure 17. Recrystallization of Phenyl Substituted Quinolinone to Highly Enantioenriched Form.....	45
---	----

Figure 18. Irreversible Oxidation of an Envisioned Quinolinone Product.....	46
--	----

List of Schemes:

Scheme 1: General Scheme of an Enantioselective Reaction Catalyzed by a Chiral Metal/Ligand Complex.....	2
Scheme 2: Types of Enantioselective Transformations.....	4
Scheme 3: The Preparation of C1-Symmetric Binaphthyl P, X-Heterodonor Ligand (R)-MOP.....	5
Scheme 4: Early Aminations: Aminotin Couplings.....	8
Scheme 5: A General Buchwald-Hartwig Reaction.....	8
Scheme 6: First Example of a Catalytic Intramolecular Amination.....	10
Scheme 7: Example of a Catalytic Intramolecular Amination Reaction.....	11
Scheme 8: Improved Intramolecular Amidations.....	12
Scheme 9: Intramolecular Amidation with Microwave Heating.....	12
Scheme 10: Intramolecular Amidation with Phenyl-naphthyl Phosphines.....	13
Scheme 11: Two Step Ugi-4CR and Intramolecular N-Arylation.....	14
Scheme 12: Example of a Two Step Ugi-4CR and Intramolecular N-Arylation..	14
Scheme 13: Traditional Amination and Amidation Reactions.....	15
Scheme 14: A Milder Ullmann Ligand Supported C-N Coupling.....	16
Scheme 15: Intramolecular Mild Ullmann coupling.....	17
Scheme 16: Ligand Free Intramolecular Mild Ullmann Amination.....	18
Scheme 17: Intramolecular Mild Ullmann Amination.....	18
Scheme 18: Tandem Intramolecular Vinyl Amidation.....	19
Scheme 19: Arylations with Nucleophiles other than Nitrogen.....	20
Scheme 20: Retention of Chirality.....	21
Scheme 21: Intramolecular Chiral Amine Couplings.....	22

Scheme 22a: Mono N-Arylation of DACH.....	22
Scheme 22b: Mono N-Arylation of DPED.....	23
Scheme 23a: Kinetic Resolution of Racemic Axially Chiral Amines.....	23
Scheme 23b: Kinetic Resolution of Racemic Axially Chiral Amines.....	24
Scheme 24: Kinetic Resolution of Dibromocyclophane 17.....	24
Scheme 25: Enantioselective N-Arylation: Resolution of Racemic Benzylamines.....	25
Scheme 26: Enantioselective N-Arylation: Generation of a Chiral Axis.....	25
Scheme 27a: Enantioselective N-Allylation: Generation of a Chiral Axis.....	26
Scheme 27b: Enantioselective N-Allylation: Generation of a Chiral Axis.....	26
Scheme 28: A General Desymmetrization of an Achiral Compound.....	27
Scheme 29a: Desymmetrization of <i>Meso</i> Dinitrogen Compounds.....	28
Scheme 29b: Desymmetrization of <i>Meso</i> Dinitrogen Compounds.....	28
Scheme 30: Example of an Enantioselective Hydroamination Reaction.....	29
Scheme 31: Malonamide Desymmetrization with an Enzyme Catalyst.....	30
Scheme 32: Condition for α -Amino Acid Synthesis.....	30
Scheme 33: Envisioned Asymmetric N-Arylations.....	31
Scheme 34: Photocyclization of N-Acylanilide.....	32
Scheme 35: Reaction Conditions.....	32
Scheme 36: Reaction Conditions for the Preparation of Malonamides.....	34

List of Tables:

Table 1. Synthesized Malonamide Derivatives and their Precursors.....	34
Table 2. Initial Experiments with Racemic BINAP.....	36
Table 3. Enantiopure Ligand Screen.....	38
Table 4. Solvent and Base Screen.....	40
Table 5. Determination of Catalyst Loading with (<i>R</i>)-MOP as Ligand.....	40
Table 6. Effect of the Size and Nature of the Nitrogen Substituent on Enantioselectivity.....	41
Table 7. HPLC Elution Conditions and Retention Times.....	43
Table 8. Intramolecular Vinyl Amidations with Copper Catalysts.....	47
Table 9. Attempted Intermolecular Aryl Amidation Experiments.....	48

List of Abbreviations:

Ac	acetyl
t-Am	<i>tert</i> -amyl (2-methyl-2-butyl)
AN	1-naphthyl
Ar	aromatic
BINAM	2,2'-Bis(N-diphenylphosphinoamino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
H8-BINAP	2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
Bn	benzyl
BrBn	2-bromobenzyl
BrV	2-bromo-2-propenyl
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl (2-methyl-2-propyl)
Boc	<i>tert</i> -Butyloxycarbonyl
Cat	catalyst
Cbz	carbobenzyloxy
DACH	1,2-diaminocyclohexane
DCM	dichloromethane
Db	dibenzylideneacetone
de	diastereomeric excess
DEM	diethylmalonate
DEMM	diethylmethylnalonate
Dppf	1,1'-bis(diphenylphosphino)ferrocene
DMA	2,6-dimethylphenyl

DMEDA	N,N'-dimethylethylenediamine
DMSO	dimethylsulfoxide
DPED	1,2-diphenylethylenediamine
DPP	diphenyl pyrrolidine-2-phosphonate
ee	enantiomeric excess
EG	ethylene glycol
eq	equivalent
h	hour(s)
HPLC	high performance liquid chromatography
L	ligand
Me	methyl
MeCN	acetonitrile
mp	melting point
mol	mole(s)
MOP	2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
PMB	4-methoxybenzyl
Ph	phenyl
PHANEPHOS	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
<i>i</i> -Pr	<i>iso</i> -propyl
RT	room temperature
SEGPPOS	5,5'-Bis[di(3,5-di- <i>t</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
SOCl ₂	thionyl chloride
ST	sealed tube

THF	tetrahydrofuran
<i>o</i> -tol	2-methylphenyl
<i>p</i> -tol	4-methylphenyl
TLC	thin layer chromatography
Tol	toluene
Trs	2,4,6-triisopropylbenzenesulfonyl
Ts	tosyl, 4-toluenesulfonyl
μW	microwave

1 INTRODUCTION

1.1 Asymmetric Synthesis

Asymmetric synthesis may be broadly defined as the synthesis of chiral compounds in the form of a single enantiomer or diastereomer.¹ Many different types of chiral compounds (**Fig.1**) can be synthesized employing varying asymmetric methodologies.

Figure 1: Types of Natural and Synthetic Chiral Compounds.

Chiral compounds may possess either (i) a centre of chirality (typically an asymmetrically substituted tetrahedral carbon atoms) ie. amino acids, (ii) an axis of chirality due to hindered rotation around a single bond most frequently occurring in allenes, biaryls and binaphthyls or (iii) a chiral plane where a substituted planar group of atoms or ring system is bridged by a linker-chain extending into the space above or below this plane restricting rotation in the molecule (**Fig.1**).²

The older methods for preparing enantiopure (enantiomeric excess or ee >99%) or enantio-enriched compounds include: (i) the classical resolution of a racemic mixture which involved the physical separation of equal mixtures of enantiomers via crystallization as diastomeric adducts, and (ii) the chiral pool approach where already chiral building blocks, usually found in nature, are transformed into new chiral products. Enantioselective syntheses where only the desired enantiomer is produced are more advantageous than resolution separations of enantiomers, in which at least 50% of the product is unused.² Methods for the

selective synthesis of enantiomers include the use of enzymes³, organocatalysts⁴ or metal catalysts.⁵

1.1.1 Enantioselective Catalysis

Enantioselective catalysis is defined as the selective synthesis of chiral compounds in the form of a single enantiomer or diastereomer from achiral reactants with the use of a chiral, non-racemic catalyst complex (**Scheme 1**).⁶

Scheme 1: General Scheme of an Enantioselective Reaction Catalyzed by a Chiral Metal/Ligand Complex.

The unique active catalyst complex is usually composed of C₂ symmetric bidentate ligands (**1**, **3**) with an axially chiral backbone containing two heteroatoms capable of coordination to a transition metal atom. However, unsymmetrical monophosphine ligands like (*R*)-MOP (**2a**) have also been proven effective for certain asymmetric transformations where only one coordination site for a phosphine ligand is available during some of the steps in the catalytic cycle.⁷ According to the hard-soft Lewis acid-base concept, soft Lewis acids tend to combine with soft Lewis bases and hard Lewis acids tend to combine with hard Lewis bases. For noble metals (soft acids), especially Os, Ir, Ru, Pd and Rh coordinating atoms include phosphorus or nitrogen atoms (soft bases) while for other metals (hard acids such as Co, Mn, Ti, B, Zn) ligands with oxygen or nitrogen atoms (harder bases) are preferred (**Scheme 2**).⁸

Figure 2. Privileged Enantioselective Ligands.

In fact, Ryoji Noyori, William Knowles and K. Barry Sharpless shared the Nobel prize in chemistry for the discovery of enantioselective catalysis. Noyori and Knowles were awarded the prize for their work on asymmetric hydrogenations (**Scheme 2**, line 1), for example, using enantiopure BINAP (**1a**), and Sharpless was honored for his work with enantioselective oxidation reactions.⁹

Since the Nobel Prize for enantioselective catalysis, a large variety of chiral ligands have been prepared and tested in a number of asymmetric transformations (**Fig.2**), but only certain classes of these synthetic catalysts are enantioselective over a wide range of mechanistically unrelated asymmetric reactions. The term "privileged ligands" has been therefore applied to certain ligands that are versatile catalysts (**2a** in **Scheme 2**).¹⁰ Screening of privileged ligands such as (**1** or **2**) allow for the discovery of novel enantioselective reactions.

Scheme 2: Types of Enantioselective Transformations.¹¹

Ligand design involves the tuning of steric (backbone) and electronic (changing donor atoms, **Figure 2: 2a-d**) properties on the ligands themselves and testing the modified versions for enhanced enantioselectivity. Specifically with axially chiral C_2 symmetrical bisphosphines it is known that the narrower the angle of the biaryl backbone upon coordination to a metal centre is known to increase enantioselectivities in certain reactions (**Figure 3**).¹²

Figure 3. Side view of (3 – SEGPHOS) showing the steric environment created by axially chiral bisphosphines where (ax, pseudo-axial position; eq, pseudo-equatorial position), and top view of the dihedral and bite angle created upon coordination to a metal.¹³

The preparation of axially chiral ligands like (*R*)-MOP developed by Hayashi is shown in **Scheme 3**.⁷ With the addition of different alkyl or aryl halides in step **b**) the ligands donor atoms can be tuned.

Scheme 3: The Preparation of C_1 -Symmetric Binaphthyl P, X-Heterodonor Ligand (*R*)-MOP. a) $\text{Ph}_2\text{P}(\text{O})\text{H}$ (2 eq.), $\text{Pd}(\text{OAc})_2/\text{dppb}$ (5 mol %), $i\text{Pr}_2\text{NEt}$, DMSO, 100°C , 14 h; b) 1) 3N NaOH, 2) MeI, K_2CO_3 ; c) $\text{HSiCl}_3/\text{Et}_3\text{N}$, xylene, 120°C , 3-5 h.

Achiral compounds with enantiotopic atoms (pro-*R* or pro-*S*) or faces (Re or Si) can be desymmetrized by a chiral catalyst that preferentially reacts with one of the enantiotopic groups (**Figure 4**). A reaction at one of the enantiotopic groups

ie. pro-R or Re-face will produce the (*R*) configuration product and vice-versa for the pro-S atom or Si-face (**Figure 4**).³

Figure 4: Symmetry Breaking of Achiral or *Meso* Compounds.

During the course of the kinetically controlled asymmetric reactions two possible transition states T_R and T_S result from the reaction of enantiotopic atoms or faces leading to the formation of two products, *S* and *R*, differing in configuration at the newly formed chirality centre. The more energetically favorable or lower the Gibb's activation energy $\Delta G^\ddagger$ for one transition state (**Figure 5**), the faster it will react and be formed in excess, thus affording the two enantiomer products in different amounts.³

Figure 5. The Course of an Asymmetric Reaction.

1.2 Carbon-Nitrogen Cross-Coupling Reactions

There are many natural products and medically important drug targets containing carbon-nitrogen bonds.¹⁴ A mild synthetic methodology that facilitates the formation of C-N bonds is of great use for the synthetic organic chemist. One such methodology, the Buchwald-Hartwig reaction has been applied in recent years towards the synthesis of various arylamines found in many antibiotics, natural products and pharmaceuticals, some of which are depicted in the figure below.¹⁵ The arrows in (**Fig.6**) point to the site where the new C-N bond was formed. Both intermolecular and intramolecular C-N cross-couplings are possible.

Figure 6: Examples of Biologically Active Compounds Synthesized via the Buchwald-Hartwig Reaction.

1.2.1 Palladium Catalyzed Buchwald-Hartwig Couplings

The first example of a palladium-catalyzed aryl amine coupling reported by Migita's group in 1983 was limited to the coupling of aminotin nucleophiles with electronically neutral aryl bromides in the presence of catalytic [(*o*-tol)₃P]₂PdCl₂ which gave aniline products in good yield (**Scheme 4**).¹⁶

Scheme 4: Early Aminations: Aminotin Couplings.

However the drawback of this discovery include a narrow reaction scope, limited to aryl bromides, and the use of tin amides which are toxic and moisture sensitive. This work went unnoticed for a decade until Buchwald and Hartwig independently discovered that the addition of a base allowed tin-free C-N couplings.¹⁶

The Buchwald-Hartwig Reaction involves the formation of a new C-N bond via the catalytic palladium-catalyzed cross-coupling of an aryl halide and a nitrogen nucleophile.¹⁷ A general Buchwald-Hartwig reaction is depicted in (**Scheme 5**):

Scheme 5: A General Buchwald-Hartwig Reaction.

The halide on the aryl group can be I, Br or Cl or a triflate (OTf), and the aryl group can contain (*o*, *m* or *p*) electron donating (alkyl, alkoxy, amino etc.) or withdrawing (carbonyl, halides, nitro, cyano etc.) groups. Many nitrogen amine

and non-amine nucleophiles can be successfully coupled with right choice of ligand, base and solvent. Amine substrates include primary alkyl or aryl amines, secondary acyclic, cyclic or diaryl amine and nitrogen containing heterocycles (indoles, pyrroles, carbazoles). Non-amine nucleophiles include amides, carbamates, sulfonamides, sulfoximines and ureas. Reactions are typically run at 80-110°C in toluene as the most popular solvent.¹⁸

The ligand is the most important component of the reaction and with palladium catalysts, phosphine ligands are most compatible. Over the years, various classes of phosphine ligands have been employed in the development of the Buchwald-Hartwig reaction (**Figure 7**). Starting with the 1st generation of simple triaryl phosphines, followed by a later more effective 2nd generation of chelating bisphosphines and concluding with a 3rd generation of Buchwald's bulky dialkyl biphenyl monophosphine ligands proving that bidentate phosphine binding is unnecessary in some cases. The large variety of phosphine ligands allow for wider screening of new reactions where a general choice between bidentate or monodentate may be trivial.^{16, 19}

Figure 7. Ligands used in Pd-Catalyzed N-Arylations.

1.2.2 Intramolecular Arylation of Amines and Amides

1.2.2.1 Intramolecular Arylation of Amines

The first example of palladium(0) mediated carbon-nitrogen bond formation using stoichiometric quantities of palladium(0) was reported by Boger in 1984 in the total synthesis of lavendamycin methyl ester.²⁰

eq. Pd(PPh ₃) ₄	Solvent	T (°C)	Time (h)	Yield (%)
0.01	THF	80 (ST)	24	0
1.0	THF	80 (ST)	20	50
1.2	THF	80 (ST)	21	81
1.5	THF	80 (ST)	21	84
1.2	Dioxane	100	20	50
1.5	Dioxane	100	24	73-80
1.2	PhMe	100	24	43

Scheme 6: First Example of a Catalytic Intramolecular Amination.

In 1997, Buchwald's group investigated Boger's work and further developed the tin-free intramolecular amination reaction, which allows easy access to a wide variety of nitrogen heterocycles. With the right choice of base and a (Ph₃P)₄Pd catalyst, five-, six-, and seven-membered nitrogen heterocycles were prepared in good yields.²¹ Amides and sulfonamides were also cyclized with the above methodology, but only to five and six-membered rings.

Scheme 7: Example of a Catalytic Intramolecular Amination Reaction.

1.2.2.2 Intramolecular Arylation of Amides

In 1999, Buchwald updated his previous protocol for the palladium-catalyzed cyclization of secondary amides or carbamates by employing chelating bidentate phosphine ligands (BINAP, Xanthphos, DPEphos) or ligands with heteroatoms capable of coordination (MOP) instead of monodentate triarylphosphine ligands.²² With the proper choice of ligand and base, five-, six-, and seven-membered rings are formed efficiently.

Scheme 8: Improved Intramolecular Amidations.

The new methodology allows the same transformations to be performed in higher yields, at decreased catalyst loadings and the formation of seven-membered rings. In another development, Poondra used sequential microwave-assisted amide synthesis and intramolecular amidation reactions as a new route to a range of N-substituted oxindoles.²³

Scheme 9: Intramolecular Amidation with Microwave Heating.

Reactions using alkylamines allow for a one-pot reaction with no need to isolate the intermediate amide. Advantages include accelerated reaction times, ability to use aryl chlorides in addition to aryl bromides, and use of anilines in addition to alkylamines, extending the range of N-substituted oxindoles that can be prepared.

Having trouble forming the five-membered benzyloxindole with MOP using Buchwald methodology, Furuta's group prepared novel phenylnaphthyl phosphines, ligands similar in structure to the MOP family for the intramolecular Pd-catalyzed aryl amidation. Two new ligands were synthesized and both ligands gave good to excellent yields in the synthesis of five-, six-, and -seven-membered rings from haloamides and carbamates.²⁴

Scheme 10: Intramolecular Amidation with Phenylnaphthyl Phosphines.

Recently, Zhu reported an elegant two-step synthesis of functionalized oxindoles involving an Ugi four-component reaction (Ugi-4CR) and the intramolecular amidation of aryl iodides with microwave heating. The Ugi-4CR reaction involved four reactants: (i) an amine, (ii) a functionalized *ortho*-iodobenzaldehyde, (iii) a carboxylic acid and an (iv) isonitrile providing α -acylaminophenylacetamide which upon an intramolecular N-arylation under appropriate conditions afforded the desired oxindole. The beauty of the Ugi-4CR is the multicomponent nature of the reaction, allowing various substituted components to be assembled.²⁵

Scheme 11: Two Step Ugi-4CR and Intramolecular N-Arylation.

Copper catalysts under the best conditions surveyed were poor with the best yield of 42 % with the intramolecular N-arylation reaction. Instead the palladium catalysts were employed for the cyclization of *o*-bromophenylacetamide as a test substrate (**Scheme 12**). The monophosphine binaphthyl ligand MOP (80%) and the biaryl bulky monophosphine Me-Phos (82%) with $\text{Pd}(\text{dba})_2$ gave the best yields. Interestingly microwave heating in toluene or toluene/acetonitrile somehow deactivated the active $\text{Pd}(\text{OAc})_2/\text{Me-Phos}$ catalyst and failed to give the cyclized oxindoles in contrast to the very good yield obtained by switching to $\text{Pd}(\text{dba})_2$.

Scheme 12: Example of a Two Step Ugi-4CR and Intramolecular N-Arylation.

1.2.3 Copper Catalyzed Ullmann and Goldberg C-N Couplings

Carbon-Nitrogen bond forming reactions before the discovery of the palladium catalyzed Buchwald-Hartwig include both the Ullmann condensation (copper-catalyzed N-arylation of amines) and the related Goldberg reaction (copper-catalyzed N-arylation of amides) which predate back to the early 1900's.²⁶ The traditional Ullmann and Goldberg reactions are depicted below (**Scheme 13**):

Scheme 13: Traditional Amination and Amidation Reactions.

The above reactions suffer from the use of stoichiometric amounts of copper reagent, high reaction temperatures and the need to use high boiling solvents and low functional group tolerance are among the main reasons that prevented these reactions from being fully exploited to their potential.²⁷

During recent years, the discovery by Buchwald that the addition of a nitrogen ligand to the traditional Ullmann or Goldberg reactions, capable of chelating to copper not only allowed for milder reaction conditions but made the reaction catalytic and greatly expanded the scope of these C-N bond forming reactions.²⁸ The milder Ullmann and Goldberg coupling reactions provide a cheaper and less toxic alternative to analogous palladium-catalyzed N-arylation of amines/amides.

Scheme 14: A Milder Ullmann Ligand Supported C-N Coupling.

Since Buchwald's introduction of chelating 1,2-diamine ligands^{28,30} in the arylation of primary and secondary amides with aryl bromides or iodides a plethora of publications followed demonstrating that a larger variety of commercially available ligands could be employed in the ligand supported milder Ullmann or Goldberg reaction, even at room temperature:

Selected examples of ligands (**Figure 8**) include: (i) diethylsalicylamide **7** in the coupling of aryl bromides with primary alkylamines³¹, (ii) ethylene glycol **8**, a diol introduced by Buchwald in the coupling of alkylamines and aryl iodides in air³² (iii) 2-picolinic acid **9** in the room-temperature α -arylation of malonates³³ (iv) Cristau introduced a Schiff base ligand ChxnPyAll **10** which allowed mild N- and C-arylation with aryl bromides and iodides (v) Ma introduced L-proline **11** as an effective ligand for mild Ullmann couplings³⁴ (vi) Roa showed that diphenyl pyrrolidine-2-phosphonate **12** (DPP) could be used in the arylation of alkyl and arylamines³⁵ (vii) copper(I)-phenanthroline **13** complexes have been utilized in the amination and amidation of aryl iodides³⁶ (viii) Roa also introduced pipercolinic acid **14** for the N-arylation of amines, amides and nitrogen-containing heterocycles.³⁷

Recently Mao used hippuric acid **15** as a new ligand for coupling aryl halides with nitrogen-containing heterocycle³⁸ while Buchwald used pyrrole 2-carboxylic acid **16** in the monoarylation of anilines with aryl iodides and bromides.³⁹

Figure 8: Structures of Ligands for Milder Ullmann/Goldberg C-N Couplings.

1.2.3.1 Intramolecular Arylation of Amines with Copper

In 2002, Buchwald's introduction of 1,2-diamine ligands allowed the first mild Ullmann copper catalyzed intramolecular aryl amidation of aryl bromides and chlorides.²⁸ For example, utilizing DMEDA (N,N'-dimethylethylenediamine) as the ligand, five-membered ring cyclization of an aryl bromide proceeded at room temperature in quantitative yield while the same cyclization with aryl chlorides required heating at 100°C for 23 hours.

Scheme 15: Intramolecular Mild Ullmann coupling.

After Buchwald's publication with DMEDA, Fukuyama's group reported a mild ligand-free procedure for the intramolecular aryl amidation of aryl bromides and iodides using a large excess of copper iodide (2 eq.) and cesium acetate (5 eq.). The reaction proceeded at room temperature with primary or N-benzyl amines

and at moderately elevated temperatures with other amine derivatives. The reaction has been applied to the formation of 5-, 6-, and 7-membered rings.⁴⁰

Scheme 16: Ligand Free Intramolecular Mild Ullmann Amination.

Later Buchwald disclosed that various commercially available β -diketones are effective supporting ligands in the copper catalyzed amination reactions. Application of one such ligand allowed the rapid intramolecular amination of aryl bromides at room temperature while aryl chlorides require a longer reaction time and heating at 60°C. It was noted that the reaction of the aryl bromide substrate could undergo cyclization in the absence of a ligand with a reaction time of 3h. On the other hand, the aryl chloride substrate could be diverted towards intermolecular cross-coupling with the addition of an aryl iodide (not shown).⁴¹

Scheme 17: Intramolecular Mild Ullmann Amination.

1.2.3.2 Intramolecular Arylation of Amides with Copper

Lautens reported the first example of a CuI-catalyzed tandem intramolecular vinyl amidation forming substituted imidazoindolones from readily accessible *ortho*

gem-dibromovinylanilines utilizing racemic DACH (diaminocyclohexane) as the ligand in refluxing toluene.^{15d} Apparently, a Pd/phosphine based system utilizing $\text{Pd}_2(\text{dba})_3/\text{Xantphos}$ ⁴² was unsuccessful in the tandem intramolecular cyclization but gave the singly cyclized 2-bromoindole in moderate yield.

Scheme 18: Tandem Intramolecular Vinyl Amidation.

Imidazoindolones are present as the key structural motif in the core structures of several biologically active compounds including the family of antifungals, fumiquinazolines, and the potent cholecystokinin antagonist aspercilin (see boxed region for a general imidazoindolone ring system in **figure 9**.^{15d}

Figure 9: Potential Bonds Formed with the Tandem Intramolecular Vinyl Amidation.

1.2.4 Other Developments

1.2.4.1 Heteroatom-Aryl Coupling

Buchwald's introduction of bulky, electron-rich *o*-biphenyl monophosphine ligands (**Figure 10**) greatly expanded the reaction scope allowing the formation of an acidic carbon-aryl bond.

Figure 10: Buchwald's Biaryl Ligand Family.

Many publications followed allowing the successful α -arylations of ketones⁴³, esters⁴⁴, amides⁴⁵, nitroalkanes and nitriles (**Scheme 19**).⁴⁶

Scheme 19: Arylations with Nucleophiles other than Nitrogen.

Since Buchwald's biphenyl ligands are not chiral (the two substituents on the aryl ring, R^1 in **figure 10**, need to be different for axial chirality) and cannot be pursued in investigating enantioselective C-N arylation reactions.

1.3 Enantioselective Cross-Coupling of Nitrogen Nucleophiles

At first glance, there may seem to be little opportunity for enantioselectivity in these reactions, since they form a bond between a nitrogen atom with pyramidal geometry (which usually undergoes rapid inversion at room temperature) and a planar sp^2 hybridized achiral carbon atom (**Fig. 11**).²

Figure 11: Inversion of Configuration at the Nitrogen Centre.

Because of this rapid interconversion, a nitrogen atom is very rarely a configurationally stable chiral centre. However, in spite of this, there are ways to break symmetry employing enantioselective N-arylations to produce chiral products from achiral starting materials. Indeed, this area of asymmetric synthesis is relatively unexplored and ripe with possibilities.

1.3.1 Chiral Amine couplings

Chiral amine couplings are possible with palladium but the reaction retains the original stereochemistry rather than create new chiral centres in the product (**Scheme 20**). Buchwald has shown that racemic BINAP is effective in the preparation of enantioenriched primary amines without racemization. No experiments were reported with enantiopure BINAP.⁴⁷

Scheme 20: Retention of Chirality.

Scheme 23b: Kinetic Resolution of Racemic Axially Chiral Amines.

Rossen from the Merck group has also reported an unusual kinetic resolution of a racemic mixture of dibromocyclophane (**17**) through the undesired arylation with benzylamine (**Scheme 24**).⁵⁰ Enantiopure bisphospine (R) -BINAP (axially chiral) was a poor ligand for this reaction in terms of reaction rate and selectivity, while enantiopure (S) -Phanephos (planar chirality) with a reaction rate seven times faster, allowed for the kinetic resolution of the (S) enantiomer. The reaction produced a complex mixture of side products leaving behind the unreacted (R) enantiomer which could be kinetically resolved as it reacts 3-4 times slower than the (S) enantiomer at 50°C.⁵⁰

Scheme 24: Kinetic Resolution of Dibromocyclophane **17**.

In the last example, using a large excess of amine (19 eq), Ohta in 2005 has reported a kinetic resolution of a racemic mixture of 1-(1-naphthyl)ethylamine by the preferential arylation of the (R) configuration enantiomer from a racemic mixture using chiral (S) -Tol-BINAP- $\text{Pd}(0)$ catalyst system (**Scheme 25**).⁵¹

Scheme 25 : Enantioselective N-Arylation: Resolution of Racemic Benzylamines.

Alternatively in 2005 reported by Taguchi the use of (S) -DBTM-SEGPHOS- $\text{Pd}(0)$ as the chiral catalyst complex, allowed the generation of a new chiral axis via the arylation of bulky anilides which blocked rotation around the C-N bond (**Scheme 26**).⁵²

Scheme 26: Enantioselective N-Arylation: Generation of a Chiral Axis.

1.3.3 Enantioselective N-Allylation

Analogous to the previous example using the same chiral ligand (*S*)-Tol-BINAP, Taguchi in 2002 also reported the first enantioselective allylation of bulky *N*-[*o*-(*tert*-butyl)phenyl]amides with allyl acetate to afford axially chiral *N*-allylanilides in excellent chemical yields (>90%), however with low enantioselectivities (**Scheme 27a**).⁵³

Scheme 27 a): Enantioselective N-Allylation: Generation of a Chiral Axis.

Around the same time (2003 publication), Curran independently reported the same enantioselective N-allylation reaction using similar conditions with chiral (*S*)-BINAP-Pd(II) catalytic complex, but still with low enantioselectivities (**Scheme 27 b**).⁵⁴

Scheme 27 b): Enantioselective N-Allylation: Generation of a Chiral Axis.

It should be noted that although the enantioselective N-allylation (reported in 2002) reaction is not classified as a Buchwald-Hartwig reaction (coupling of an allyl group instead of an aryl group to a nitrogen) it appears that the enantioselective N-arylation (2005) reaction was modeled after the former enantioselective N-allylation.

A final way to create a chiral product from an asymmetric Buchwald-Hartwig reaction with nitrogen nucleophiles involves the desymmetrization of achiral or *meso*-dinitrogen nucleophiles by selective N-arylation (enantiocontrol of prochiral nitrogen atoms) see **Scheme 28**.

Scheme 28: A General Desymmetrization of an Achiral Compound through Preferential Arylation of one of the (b) Atoms in the Molecule. The Atoms Marked as (b) Represent Nitrogen Atoms.

To the best of the authors knowledge, the literature contains no examples of the desymmetrization of achiral dinitrogen compound through an asymmetric N-arylation to generate new chiral products.

However, there has been a rare and recent example of catalytic asymmetric desymmetrization of *meso*-diamide derivatives through an enantioselective N-allylation with a chiral catalyst $\{Pd(-C_3H_5)Cl_2\}/(R,R)$ -Trost catalyst.⁵⁵ The enantioselectivity observed in the desymmetrization of *meso*-N-N' substituted dinitrogen with allyl acetate were excellent and were dependent on the nature of the R group (**Scheme 29 a**).

Scheme 29 a): Desymmetrization of *Meso* Dinitrogen Compounds.

The reversal of enantioselectivity was observed by replacing the (Trs) with a Tosyl (Ts) substituent on a nitrogen atom. Enantioselectivity was influenced by the temperature with improvement in enantioselectivity observed at a lower temperature (**Scheme 29 b**).⁵⁵

Scheme 29 b): Desymmetrization of *Meso* Dinitrogen Compounds.

1.3.4 Enantioselective Hydroamination

In a palladium catalyzed asymmetric hydroamination reaction, Hartwig has prepared chiral, nonracemic amine products from achiral arylamine coupling to vinylarenes. The chiral products gave the highest ee's ever reported for this reaction.⁵⁶

Scheme 30: Example of an Enantioselective Hydroamination Reaction.

While this is an interesting and effective enantioselective formation of a C-N bond, it is formally an asymmetric addition reaction, rather than an asymmetric substitution reaction as in the cross-coupling chemistry in which we are interested.

1.3.5 Enzymatic Desymmetrization of α,α -Disubstituted Malonamides

Li has reported a novel enzymatic desymmetrization of a variety of α,α -disubstituted malonamides with a highly enantioselective biocatalyst, an amidase enzyme (*Rhodococcus* sp CGMCC 0497).⁵⁷ The enantioselective enzymatic hydrolysis of one nitrogen gave access to challenging enantiopure α,α -disubstituted malonamic acids with up to >99% ee and 98% chemical yields. Selected examples are shown below in (**scheme 31**)

Scheme 31: Malonamide Desymmetrization with an Enzyme Catalyst.

The desymmetrization of malonamides has applications in further synthesis of chiral α -amino acids.⁵⁸ In fact the chiral products in the above reaction could be converted to valuable (*R*) or (*S*)- α,α -dialkylated amino acids using routine procedures.⁵⁷

Scheme 32: Condition for α -Amino Acid Synthesis: (a) DMF, EtBr, K_2CO_3 , rt; (b) DMF, $Hg(OAc)_2$, NBS, EtOH, rt; (c) 20% HCl, reflux; (d) P_2O_5 , PhMe; (e) 2N NaOH, THF, rt; (f) $SOCl_2$, NaN_3 , MeOH.

1.4 Applications

We envision the asymmetric intra- and intermolecular Buchwald-Hartwig N-arylation of various malonamide derivatives as preliminary literature examples for purposes of accessing existing and novel chiral aryl amines and amides which are valuable structural units found in various natural products, pharmaceuticals and agrochemicals. An enantioselective N-arylation route to chiral oxindoles^{23, 45,}

⁵⁹ (5-membered ring) and quinolinones (six-membered ring) would be a useful reaction in the synthesis of natural products. The tetrahydroquinolinone derivative is envisioned to be a precursor of chiral buchapine (**Scheme 33**) an anti-HIV natural product.⁶⁰ Of course cyclizations to form larger seven- and eight-membered rings are theoretically possible with application in natural product synthesis. An enantioselective intermolecular N-arylation could potentially be used to synthesize chiral ligands with applications in asymmetric synthesis.^{57, 61}

Scheme 33: Envisioned Asymmetric N-Arylations.

Methods for the convenient synthesis of the necessary malonamide cyclization precursors need to be developed first prior to any investigation of the enantioselective N-arylation reactions.

The literature contains two examples of similar cyclic lactam products we envision with the asymmetric N-arylation. In the first example, back in the 1980's,

utilizing a photocyclization reaction, Ninomiya irradiated N-acylanilide substituted with $-\text{CONH}_2$ groups causing a 1,5-migration of the ortho-substituents that resulted in a mixture of products (**Scheme 34**).⁶² The compound highlighted in red is similar in structure to one of the envisioned cyclic compounds (**Scheme 33**).

Scheme 34: Photocyclization of N-Acylanilide.

In the other example, Ignatchenko produced the desired compound 3-methylaminocarbamoyl-N-methyl-2-quinolone (highlighted in red) in poor yield (7%) via an isomerizing recyclization of a quaternary salt of diethyl 2-(2-pyridyl)ethylmalonate (the Kost-Sagitullin reaction), itself derived from the reaction between diethylmalonate (DEM) and 2-vinylpyridine as shown in **scheme 35**.⁶³

Scheme 35: Reaction Conditions: a) 1. EtOH/metallic sodium, 2h; 2. evaporate; 3. H^+ , b) MeI, c) $\text{MeNH}_2/\text{H}_2\text{SO}_3$.

2 RESULTS AND DISCUSSION

2.1 Synthesis of Malonamide Precursors

Access to malonamides (**3**) (**Scheme 36**, **Table 1**, entries 12-27) was achieved following standard literature procedures.⁶⁴ Diethyl malonate (**DEM**) (entries 1-2, 5) or diethyl methylmalonate (**DEMM**) (entries 3-4,6) was deprotonated with sodium hydride and alkylated in good yield with either benzyl bromide (entry 3), 2-bromobenzyl bromide (entries 1, 4-5) or 2,3-dibromopropene (entries 2,6). Diester (**1**) was saponified and then acidified (cold, to prevent decarboxylation), affording diacid (**2**) in excellent yield. This was converted to the diacid chloride by treatment with thionyl chloride, and then used directly in the preparation of malonamides (**3**) (**Table 1**, entry 12-27) in moderate yields.

DEM: R¹ = H DEMM: R¹ = Me

Scheme 36: Reaction Conditions for the Preparation of Malonamides a) NaH, R²Br, THF reflux, o/n; b) (i) 4N NaOH, MeOH reflux, o/n, (ii) H⁺, 0°C; c) (i) SOCl₂, 4h, (ii) Evaporate, (iii) R³NH₂, NEt₃ DCM or THF o/n

Entry	Product	R ¹	R ²	R ³	Yield [%]
1	1	H	BrBn ^[a]	/	91
2	1	H	BrV ^[b]	/	52
3	1	Me	Bn	/	> 100 ^[c]
4	1	Me	BrBn	/	97
5	1	BrBn	BrBn	/	86
6	1	Me	BrV	/	> 100 ^[c]
7	2	H	BrBn	/	81
8	2	H	BrV	/	35
9	2	Me	Bn	/	72
10	2	Me	BrBn	/	92
11	2	Me	BrV	/	72
12	3	H	BrBn	<i>t</i> -Bu	16
13	3	H	BrBn	Bn	39
14	3	H	BrV	<i>t</i> -Bu	17
15	3	H	BrV	Bn	14
16	3	Me	Bn	Bn	51
17	3	Me	BrV	<i>t</i> -Bu, H	12
18	3	Me	BrV	Bn	77
19	3	Me	BrBn	H	50
20	3	Me	BrBn	Me	51
21	3	Me	BrBn	<i>i</i> -Pr	36
22	3	Me	BrBn	<i>n</i> -Bu	50
23	3	Me	BrBn	Ph	72
24	3	Me	BrBn	Bn	74
25	3	Me	BrBn	PMB ^[d]	37
26	3	Me	BrBn	DMA ^[e]	16
27	3	Me	BrBn	AN ^[f]	30

Table 1. Synthesized Malonamide Derivatives and their Precursors.

[a] BrBn = 2-bromobenzyl; [b] BrV = 2-bromo-2-propenyl; [c] crude reaction without purification; [d] PMB = 4-methoxybenzyl; [e] DMA = 2,6-dimethylphenyl; [f] AN = 1-naphthyl

An alternative route towards the preparation of malonamides (3) was attempted.⁸¹ The direct amidation of the dialkylated diester (5) by benzyl amine in the presence of trimethylaluminum (AlMe₃) in THF at 40°C for 48h failed to produce the diamide. It is unclear as to why this direct route failed to give the diamide, perhaps could be attributed to the doubly alkylated ester with two bromobenzyl groups at the position sterically restricted the reaction. It should be noted that the literature reaction involved a different malonate and anhydrous DCM was employed.

A double alkylated malonamide derivative with 2-bromo-benzylbromide at the α position was also envisioned for a double intramolecular cyclization. However precursors, the dialkylated diester (Table 1, entry 5) which was made in good yield (86%) failed to hydrolyze to give the corresponding dialkylated diacid.⁶⁵

2.2 Intramolecular Aryl Amidation of 2-(2-Bromobenzyl)malonamides

In order to optimize the intramolecular Buchwald-Hartwig N-arylation reaction of various malonamide derivatives, initial experiments were conducted with the benzyl substituted malonamide using a catalyst system based on racemic BINAP as a cost saving measure and 2-(2'-bromobenzyl)-N,N'-dibenzyl-2-methylpropanediamide as the test substrate. (Table 2). The best result²² from this initial screening (not shown) involved the use of 3.3 mol% Pd(OAc)₂, 5 mol% BINAP, 1.4 eq. Cs₂CO₃, heating at 100 °C in toluene for 16 hours, which afforded the desired racemic quinolinone (*N*,1)-dibenzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide in 94% yield (entry 1). Performing the reaction on a 0.65 and 3.0 mmol scale respectively also gave excellent yields (entries 2 and 3). It was noted that the above failed to give the cyclized product (i) without added ligand, (ii) in DMF as solvent and (iii) when the temperatures were below 90 °C in toluene. It was important to let the ligand, metal and malonamide dissolve at 100 °C first before adding the base as noted by Buchwald.²²

Entry	Metal	Ligand	Base	Solvent	mmol	Yield [%]
1	Pd(OAc) ₂	(+/-) BINAP	Cs ₂ CO ₃	Toluene	0.1	94
2	Pd(OAc) ₂	(+/-) BINAP	Cs ₂ CO ₃	Toluene	0.65	88
3	Pd(OAc) ₂	(+/-) BINAP	Cs ₂ CO ₃	Toluene	3	87
4	Pd(OAc) ₂	none	Cs ₂ CO ₃	Toluene	0.1	NR
5	Pd(OAc) ₂	(<i>R</i>)-BINAP	Cs ₂ CO ₃	DMF	0.1	NR
6	Pd(OAc) ₂	(<i>R</i>)-BINAP	Cs ₂ CO ₃	Toluene	0.25	85

Table 2. Initial Experiments with Racemic BINAP.

Having success with racemic BINAP, it was logical to employ the enantiopure (*R*)- or (*S*)-BINAP as ligand in the enantioselective version of the intramolecular aryl amidation. The reaction gave the same yield as racemic BINAP as expected while the enantiomeric ratio was 4:3 in favour of one enantiomer. The preliminary results show that axially chiral phosphine ligands have enantioselective potential.

In an effort to improve the enantioselectivity in the intramolecular aryl amidation, a variety of ligands, solvents and bases were screened with benzylmalonamide as a test substrate.

First, as summarized in (Table 3) a small selection of chiral phosphine ligands (Figure 12) widely utilized in enantioselective synthesis were screened.

Figure 12. Structures of Chiral Phosphines utilized in the Ligand Screen.

The ligands examined include (i) C₂-symmetric axially chiral bisphosphine ligands: (*S*)-CTH-BINAM (entry 1); (*R*)-BINAP (entry 2); (*R*)-xylyl-BINAP (entry 3); (*R*)-H8-BINAP (entry 4); and (*R*)-DTBM SEGPHOS (entry 5), (ii) the C₁-symmetric axially chiral monophosphine: (*R*)-MOP (entry 7) and lastly (iii) (*S*)-PHANEPHOS which exhibits planar chirality (entry 6).

In general, bisphosphine ligands have been regarded as more effective than monophosphine ligands in constructing a chiral environment by coordination to a metal and thus enhancing enantioselectivity.⁶⁶ In fact, one of the most effective chiral bisphosphine ligands BINAP imparts high enantioselectivity in several asymmetric reactions including rhodium or ruthenium-catalyzed hydrogenation.⁶⁷ In our case, the worst result occurred with (*R*)-BINAM (entry 1), a successful ligand utilized in the enantioselective, rhodium-catalyzed hydrogenation of α -phenylenamides⁶⁸ failed to give any cyclized product in the reaction (entry 1). It appears that the phosphinoamino substituent of the 1,1'-binaphthalene framework somehow hinders this reaction. An improvement in enantioselectivity was observed with the BINAP family of ligands. Depending on the type of asymmetric reaction one type of BINAP derivative often gives better enantioselectivities than

BINAP. For example the H8-BINAP ligand, as the ruthenium complex, catalyzes hydrogenation of unsaturated carboxylic acids to a higher ee than does BINAP.⁶⁹ However in this case all three ligands (*R*)-BINAP, (*R*)-xylyl-BINAP, (*R*)-H8-BINAP gave low enantioselectivities (11-13 %) (**entries 2-4**). The other axially chiral bisphosphine ligand, DTBM SEGPHOS^{12c} with a very narrow dihedral angle also gave poor ee values (**entry 5**).

Entry	Enantiopure Ligand	Yield [%]	ee [%]
1	CTH-(<i>S</i>)-BINAM	NR	/
2	(<i>R</i>)-BINAP	85	13
3	(<i>R</i>)-xyl BINAP	65	12
4	(<i>R</i>)-H8 BINAP	36	11
5	(<i>R</i>)-DTBM-SEGPHOS	62	5
6	(<i>S</i>)-PHANEPHOS	51	6
7	(<i>R</i>)-MOP	85	57

Table 3. Enantiopure Ligand Screen.

Interestingly, (*R*)-MOP (entry 7) provided much higher enantioselectivity than the *C*₂-symmetric bisphosphines (entries 2-5). The 44% ee enhancement observed with (*R*)-MOP over (*R*)-BINAP which gave the best ee of the other bisphosphines screened (entry 7 vs. entry 2), can be attributed to MOP's ability to monocoordinate palladium. It is already known that the *C*₁ symmetric (*R*)-MOP ligand allows versatile co-ordination to palladium, acting as a monophosphine or P,C-bidentate ligand in Pd(0)-catalyzed asymmetric allylic substitutions.⁷⁰ Also the OMe group could be weakly chelating (P,O-bidentate coordination). In our case it is proposed that (*R*)-MOP is monocoordinating to palladium, opening up a

coordination site which may play a role in the enhanced enantioselectivities observed.

Also, Buchwald found that the (+/-)-MOP ligand was superior relative to BINAP and DPEphos in the intramolecular cyclization of aryl bromides with secondary amides for the formation of seven-membered ring tertiary amides. The second ligating group OMe on MOP is only weakly chelating with palladium, increasing the Pd-P bond length and resulting in an open coordination site.⁷¹ It suggests that an open coordination site may be necessary in the coordination of the secondary amide to the putative Pd(II) oxidative addition complex to form an eight-membered palladacycle intermediate.²²

To summarize, the low enantioselectivities observed with the chelating bisphosphine ligands are due to their low catalytic activity and/or low selectivity toward the intramolecular aryl amidation reaction pathway. Noyori observed that for certain asymmetric reactions, chelating bisphosphine ligands are incompatible with the catalytic reactions where the catalyst can provide only one coordination site for a phosphine ligand during some of the steps in the catalytic cycle (**Figure 14**).⁷ Thus, the chiral monodentate phosphine ligand (*R*)-MOP is required for the realization of a high level of enantioselectivity and was utilized as the ligand in further optimization experiments.

A further solvent and base screen (**table 4**) with benzylmalonamide as the test substrate again, revealed that THF was the best solvent in terms of yield and enantioselectivity (entry 1-4 vs. entry 5) while Cs₂CO₃ and K₃PO₄ provided the best balance between yield and enantioselectivity (entry 5 and 9). The lower refluxing reaction temperature (65°C) of THF is attributed to the observed enhancement in enantioselectivity. Another solvent, *t*-BuOH that was recently reported to be optimal for solubilizing amides and /or deprotonated amides could potentially be screened in the future.⁷²

Entry	Solvent	Temperature	Base	Yield [%]	% ee
1	Toluene	110°C	Cs ₂ CO ₃	82%	30%
2	Dioxane	100°C	Cs ₂ CO ₃	96%	55%
3	DMSO	100°C	Cs ₂ CO ₃	30%	8%
4	MeCN	81°C	Cs ₂ CO ₃	14%	35%
5	THF	65°C	Cs ₂ CO ₃	95%	57%
6	THF	65°C	NaOAc	25%	54%
7	THF	65°C	NaOt-Am	35%	39%
8	THF	65°C	K ₂ CO ₃	31%	65%
9	THF	65°C	K ₃ PO ₄	96%	57%
10	THF	65°C	KOt-Bu	70%	69%

Table 4. Solvent and Base Screen.

Next the amount of catalyst loading with varying ratios of (*R*)-MOP to Pd was investigated and a 1:2 ratio was found to be optimal (**Table 5**, entry 3).

L (Ligand)	Pd(OAc) ₂	L/Pd ratio	Yield	% ee
3.3	3.3	1	69	48
5	3.3	1.5	85	48
6.6	3.3	2	70.5	54
9.9	3.3	3	58.6	51

Table 5. Determination of Catalyst Loading with (*R*)-MOP as Ligand.

In order to determine the effect of the size and nature of the nitrogen substituent on enantioselectivity a variety of alkyl and aryl malonamides were synthesized (**Table 6**) and used in the intramolecular aryl amidation on a larger scale (100 mg). It was originally hypothesized that increasing the steric bulk on nitrogen would improve enantioselectivity. For the alkyl substituents, the enantioselectivity does in fact increase with increased bulk: Me (38% ee) < *n*-Bu (49% ee) < *i*-Pr (70% ee). A trend could not be determined with the aryl substituents, since the 2,6-dimethylphenyl substituted quinolinone **2g** co-eluted with the bromide precursor, and the naphthyl compound **2h** seems to have been a mixture of diastereomers (discussed below).

Product	R	Base	Yield	ee ^[a]
2a	Me	Cs ₂ CO ₃	>99%	27%
2a	Me	K ₃ PO ₄	>99%	38%
2b	<i>n</i> -Bu	Cs ₂ CO ₃	>99%	49%
2c	<i>i</i> -Pr	K ₃ PO ₄	90%	70%
2d	Bn	Cs ₂ CO ₃	>99%	55%
2d	Bn	K ₃ PO ₄	>100%	57%
2e	4-methoxybenzyl	Cs ₂ CO ₃	>99%	75%
2e	4-methoxybenzyl	K ₃ PO ₄	57% ^[b]	48%
2f	Ph	Cs ₂ CO ₃	>99%	58%
2g	2,6-dimethylphenyl	Cs ₂ CO ₃	ND*	ND*
2g	2,6-dimethylphenyl	K ₃ PO ₄	~54% ^[c]	ND*
2h	1-naphthyl	Cs ₂ CO ₃	43%	ND*
2h	1-naphthyl	K ₃ PO ₄	79%	ND*

Table 6. Effect of the Size and Nature of the Nitrogen Substituent on Enantioselectivity. [a] Determined by chiral HPLC (CHIRALCEL OD-H column), average of three runs, [b] yield losses during work-up. [c] Calculated based on NMR integration of the mixture.

The enantioselectivity was found to be moderately sensitive to the base and or

solvent. For example in refluxing THF, K_3PO_4 appears to give slightly higher ee's with the methyl malonamide 38% (K_3PO_4) vs. 26% (Cs_2CO_3), whereas the opposite was observed for the 4-methoxybenzyl malonamide where the reaction with Cs_2CO_3 gave a 27% ee enhancement over K_3PO_4 . No real difference in ee was seen with the 2,6-dimethylphenyl substituted malonamide when either base was employed ie. 22% (K_2CO_3) vs. 23% (Cs_2CO_3). The effect of the nature of the Cs^+ or K^+ counterion in this reaction is unclear. Also, the reaction of the phenyl malonamide in THF (58% ee) was much lower than the identical reaction in toluene (75% ee) while the opposite effect was observed with the isopropyl malonamide 70% ee in THF and 63% ee in toluene (data not shown).

The ee for the naphthyl substituted quinolinone (**Table 6**) could not be determined since the product was isolated as an inseparable mixture of diastereomers due to a new chiral axis arising from restricted rotation about the N-naphthyl axis (**Figure 13**).

Figure 13. Inseparable Diastereomers of Naphthyl Substituted Quinolinone.

The reversal of enantioselectivity was observed depending on the nature of the substituent on the nitrogen atom. The major enantiomer as determined by chiral HPLC of malonamides with both the benzyl and 4-methoxybenzyl substituents (**Table 7**, entry 5 and 6) eluted second whereas for the rest of the substituents (**Table 7**, entry 1-4) the major enantiomer eluted first (compare retention times of major vs. minor enantiomers).

Entry	R	$t_R(\text{minor})^{[a]}$	$t_R(\text{major})$	eluent (%IPA) ^[b]
1	Me	25.6	17.9	13
2	n-Bu	17.6	12.9	3
3	i-Pr	25.4	21	1
4	Ph	16.7	15.3	10
5	Bn	18.1	23.8	20
6	PMB ^[c]	31.2	36.4	20
7	DMA ^[d]	16.9	13.3	8
8	AN ^[e]	N/D	N/D	17

Table 7. HPLC Elution Conditions and Retention Times

[a] t_R = Retention time of major and minor enantiomer measure in minutes [b] Eluent = % of isopropanol in hexanes, [c] PMB = 4-methoxybenzyl, [d] DMA = 2,6-dimethylphenyl (we cannot exclude the possibility that one of the peaks is the bromide starting material since this was not effectively separated from the quinolinone product), [e] AN = 1-naphthyl

Without X-ray absolute structure determination it is unclear as to which enantiomer is produced in excess with (*R*)-MOP. Since both diastereomeric complexes (*R*)-ligand-(*R*)-substrate and (*R*)-ligand-(*S*)-substrate in the catalytic cycle are possible, leading to either the (*R*)- or (*S*)-products respectively (**Figure 14 and 15**). Further studies are needed to elucidate the mechanism of this reaction to determine the precise nature of co-ordination between MOP, palladium and the malonamide substrate and the effect of ligand structure (**Figure 16**) (binaphthyl vs. biphenanthyl backbone), ligand electronics (**Figure 16**) (replacing the methoxy group ie. MOP by some other atom ie. H or N) on enantioselectivities.⁷

Figure 14. Simplified Catalytic Cycle in a Pd Asymmetric Intramolecular Amidation Reaction of a Malonamide Derivative.

Figure 15. Proposed Diastereomeric Intermediates, with Monodentate (R)-MOP as Ligand.

Figure 16. Tuning of steric or electronic properties of MOP Ligands.

The phenyl substituted quinolinone, originally formed in 58% ee, (**Table 6**) has been enantioenriched up to 99% ee through two recrystallization from CH₂Cl₂ / hexanes (**Figure 17**). Work is currently underway to determine the absolute configuration by X-Ray crystallography. Being able to correlate the configuration of the major products to that of the ligand used in the catalyst will help us to develop a model explaining the stereoselectivity in these reactions (see **Figure 15**).

Figure 17. Recrystallization of Phenyl Substituted Quinolinone to Highly Enantioenriched Form.

The intramolecular amidation was also tested with a bromobenzyl malonamide bearing no additional substituent at the α -position (**Scheme 1, entry 13**). The cyclization occurred in 77% yield with (*R*)-MOP/Pd catalyst system, however the envisioned product undergoes irreversible oxidation in air upon purification.

Figure 18. Irreversible Oxidation of an Envisioned Quinolinone Product.

2.3 Intramolecular Vinyl Amidation of Bromovinyl Malonamides

The enantioselective intramolecular vinyl amidation of bromovinyl malonamides was investigated with copper for the formation of lactams. Lautens recently reported a copper catalyzed tandem intramolecular reaction with a bromovinyl group.^{15d} The reaction undergoes the desired cyclization under Pd/MOP catalysis in low yield (**Table 8**, entry 5), while the racemic lactam was obtained in good yield under the influence of CuI and racemic 1,2-diaminocyclohexane (**Table 7**, entry 1). Next, a few enantiopure ligands were screened (**Table 8**, entry 2-4), giving better yields than racemic DACH (entry 3 and 4). The reaction with (*R,R*)-ChxnPyAll was incomplete due to an improper joint seal which lead to solvent evaporation and an incomplete reaction (entry 2). The enantiomeric excess was unable to be determined as both enantiomers of the cyclic lactam had the same retention time with the chiral columns employed.

Entry	Ligand	Yield [%]	% ee
1	<i>rac</i> -DACH	65	/
2	(<i>R,R</i>)-ChxnPyAll	27 ^[a]	nd ^[b]
3	(<i>R,R</i>)-DACH	84	nd
4	L-Proline	87	nd
5	(<i>R</i>)-MOP ^[c]	40	nd

Table 8. Intramolecular Vinyl Amidations with Copper Catalysts.

[a] incomplete reaction (solvent evaporated), the reaction was not repeated; [b] enantiomers could not be resolved on CHIRALCEL OD-H or CHIRALPAK AD-H columns eluting with 10-16 % IPA:Hexanes [c] Conditions : Pd(OAc)₂ (3.3 mol %), (*R*)-MOP (6.6 mol %), 100°C.

2.4 Intermolecular Aryl Amidation

After much success with the intramolecular aryl amidation reaction, our attention was shifted towards the intermolecular reaction. Initial experiments between α,α -disubstituted benzylamide with various aryl halides involved a screen of a variety of metals sources, ligands, bases and solvents (**Table 9**). The combinations chosen involve those reported for the coupling of acetamide with various aryl halides with copper²⁷ (entry 2 and 3) and palladium⁷³ (entry 1 and 4-9). Regardless of the metal or ligand employed, couplings with aryl bromides in general were unsuccessful and only starting material was recovered (entry 1,2,5,6). The tetradentate nitrogen ligand ChxnPyAll appeared to give the product by TLC analysis however, without NMR data for this reaction it is not possible to conclude that the arylated product was formed (entry 3). Racemic BINAP gave a mixture of products successfully purified by flash chromatography eluting with 20% EtOAc: Hexanes, however the higher *R_f* spot showed no alkyl protons in the product while the lower *R_f* spot was not analyzed by NMR for it was

inappropriately assumed that it was only starting material (entry 4). The reaction with Xantphos as ligands was unsuccessfully purified so no NMR data is available (entry 7).

Entry	Metal	Ligand	ArX	Solvent	Conc [M]	yield [%]
1	Pd ₂ (dba) ₃	Xantphos	4-BrC ₆ H ₄ CN	Toluene	0.1	nr ^[a]
2	CuI	ChxnPyAll	4-BrC ₆ H ₄ CN	Toluene	0.1	nr ^[a]
3	Cu ₂ O	ChxnPyAll	PhI	DMF	1.4	nd ^[b]
4	Pd(OAc) ₂	(+/-) BINAP	PhI	Toluene	0.25	nd ^[b]
5	Pd(OAc) ₂	(+/-) BINAP	PhBr	Toluene	0.25	nr ^[a]
6	Pd ₂ (dba) ₃	(+/-) BINAP	PhBr	Toluene	0.25	nr ^[a]
7	Pd ₂ (dba) ₃	Xantphos	PhI	Dioxane	0.25	nd ^[b]
8	Pd(OAc) ₂	(R)-MOP	PhI	Toluene	0.13	nd ^[b]
9	Pd(OAc) ₂	(R)-DBTM-SEGPHOS	PhI	Toluene	0.13	nd ^[b]

Table 9. Attempted Intermolecular Aryl Amidation Experiments.

[a] starting material recovered [b] A reaction occurred (by TLC analysis), but no product was successfully isolated.

Enantiopure ligands (*R*)-MOP proven effective for the intramolecular aryl amidation and (*R*)-DBTM-SEGPHOS were also tested with both giving a complex mixture of products that were difficult to purify (entry 8 and 9).

The above results indicate that the intermolecular aryl amidation reactions are more difficult than the corresponding intramolecular versions, similar

observations were found by other groups for the analogous Pd-catalyzed amidation reaction.^{30, 74}

It would be of interest to pursue this reaction further with copper and enantiopure ligands successful with the bromovinyl substrate.

3 EXPERIMENTAL

3.1 General Considerations

All reagents unless otherwise noted were purchased from SIGMA-ALDRICH. Enantiopure phosphine ligands were purchased from STREM CHEMICAL COMPANY. (R,R)-ChxPyAll was prepared according to literature procedures.²⁷ Potassium phosphate (K_3PO_4) was purchased from FLUKA (catalog #04347). The solvents PhMe, ACN, 1,4-dioxane, DMSO, and DMF were used straight out of anhydrous bottles. Anhydrous THF was obtained by passage through a bed of activated molecular sieves under an atmosphere of dry nitrogen. Palladium sources and bases were flushed with nitrogen after each use. All prepared malonamide derivatives were stored in glass vials at room temperature in the dark.

Melting points were uncorrected. 1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Spectrometer (Ryerson University) or a 300 MHz Varian Spectrometer (UofT). NMR spectra are referenced to an internal TMS standard or the residual $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm) solvent signal. Proton assignments were interpreted with the aid of the corresponding COSY spectra (not included) and carbon assignments were determined with the aid of HSQC and HMBC analysis (spectra not included). Mass spectra (MS) were recorded by electron impact time-of-flight (EI-TOF) or electrospray time-of-flight (ESI-TOF) ionization for novel non-literature compounds. High-performance liquid (HPLC) analysis was performed with a 25 x 0.4 cm i.d. CHIRALCEL-OD-H column with a UV detector.

3.2 Preparation of Malonamide Derivatives

Method 3.2.1 General Procedures for Malonate Ester Alkylations.^{64b, 75}

Method 3.2.1 Diethyl malonate (DEM) (1.0 eq) was added slowly by syringe to a suspension of NaH (60% dispersion in mineral oil, 1.0 eq.) in THF (0.5 M) at 0°C. The mixture was stirred for approximately 30 minutes, when hydrogen gas evolution ceased, the appropriate alkylhalide (1.1 eq) was added and the

resulting milky white mixture was refluxed over night. The solution was cooled to room temperature, diluted with ether or ethyl acetate (2 x volume of the reaction) and washed three times with water (1/2 volume of extraction solvent) directly without evaporation of THF. The organic layer was dried over MgSO_4 and concentrated in vacuo. The crude product was purified on silica eluting with 10% EtOAc/hexanes.

OR

3.2.2 Diethyl methylmalonate (DEMM) (1.0 eq) was added slowly by syringe to a suspension of NaH (60% dispersion in mineral oil, 1.1 eq.) in THF (0.5 M) at 0°C . The mixture was stirred for approximately 30 minutes, when hydrogen gas evolution ceased, the appropriate alkylhalide (1.3 eq, excess) was added and the resulting milky white mixture was refluxed over night. The solution was cooled to room temperature, diluted with ether or ethyl acetate (2 x volume of the reaction) and washed three times with water (1/2 volume of extraction solvent) directly without evaporation of THF. The organic layer was dried over MgSO_4 and concentrated in vacuo. The crude product was purified on silica eluting with 10% EtOAc/hexanes.

OR

3.2.3 Diethyl malonate (DEM) (1.0 eq) was added slowly by syringe to a suspension of NaH (60% dispersion in mineral oil, 1.0 eq.) in THF (0.5 M) at 0°C . The mixture was stirred for approximately 30 minutes, when hydrogen gas evolution ceased, 2-bromobenzylbromide (2.4 eq) was added and the reaction was refluxed over night. The solution was cooled to room temperature, diluted with ether or ethyl acetate (2 x volume of the reaction) and washed three times with water (1/2 volume of extraction solvent) directly without evaporation of THF. The organic layer was dried over MgSO_4 and concentrated in vacuo. The crude product was purified on silica eluting with 10% EtOAc/hexanes.

Diethyl (2-bromobenzyl)propanedioate - (18). This product was isolated as a clear oil in 91% yield (50 mmol scale, 14.5 g) by method 3.2.1 with 2-bromobenzylbromide as the alkyl halide; TLC (5% EtOAc:Hexanes), $R_f = 0.26$; ^1H NMR (CDCl_3 , 400 MHz) δ 7.49-7.44 (m, 1H), 7.20-7.10 (m, 2H), 7.05-6.97 (m, 1H), 4.13-4.01 (m, 4H, H11), 3.78 (t, $J = 8.0$ Hz, 1H, H2), 3.27 (d, $J = 8.0$ Hz, 2H, H3), 1.14 (t, $J = 7.0$ Hz 6H, H12). ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.7 (C1), 137.1 (Ar), 132.9 (Ar), 131.5 (Ar), 128.6 (Ar), 127.4 (Ar), 124.6 (Ar), 61.5 (C2), 51.5 (C11), 51.2 (C3), 35.1 (C12).

Diethyl benzyl(methyl)propanedioate - (19). This product was isolated as a clear oil in >100% yield (37.6 mmol scale, 14.734 g, EtOAc contaminated) by method 3.2.2 with benzylbromide as the alkyl halide; TLC (5% EtOAc:Hexanes), $R_f = 0.47$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.29-7.18 (m, 3H), 7.14-7.01 (m, 2H), 4.22-4.15 (m, 4H, H12), 3.22 (d, $J = 8.0$ Hz, 2H, H3), 1.33 (s, 3H, H10), 1.25 (t, $J = 7.0$ Hz, 6H, H13).

(20)

Diethyl (2-bromobenzyl)(methyl)propanedioate – (20). This product was isolated as a clear oil in 97% yield (29.3 mmol scale, 9.826 g) by method 3.2.2 with 2-bromobenzylbromide as the alkyl halide; TLC (5% EtOAc:Hexanes), R_f = 0.22; ^1H NMR (CDCl_3 , 400 MHz) δ 7.56-7.53 (d, J = 8.0 Hz, 1H), 7.23-7.14 (m, 2H), 7.10-7.05 (m, 1H), 4.26-4.18 (m, 4H, H12), 3.52 (s, 2H, H3), 1.39 (s, 3H, H10), 1.26 (t, J = 7.0 Hz, 6H, H13); ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.9 (C1), 136.4 (Ar), 133.1 (Ar), 131.4 (Ar), 128.5 (Ar), 127.3 (Ar), 126.3 (Ar), 61.5 (C2), 55.1 (C12), 39.3 (C3), 19.35 (C13), 14.0 (C10).

(21)

Diethyl bis(2-bromobenzyl)propanedioate – (21). This product was isolated as a clear oil in 86% yield (10 mmol scale, 4.3 g) by method 3.2.3 ; TLC (10% EtOAc:Hexanes), R_f = 0.43; ^1H NMR (CDCl_3 , 300 MHz) δ 7.52 (dd, J = 10.5 Hz, J = 2.0 Hz, 2H), 7.32 (dd, J = 10.5 Hz, J = 2.0 Hz, 2H), 7.19 (td, J = 10.0 Hz, J = 2.0 Hz, 2H), 7.09-7.02 (m, 2H), 4.08 (q, J = 7.0 Hz, 4H, H11), 3.56 (s, 4H, H3), 1.06 (t, J = 7.0 Hz, 6H, H12); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.0 (C1), 136.9 (Ar), 133.0 (Ar), 131.9 (Ar), 128.5 (Ar), 127.4 (Ar), 126.6 (Ar), 61.8 (C2), 59.6 (C11), 39.2 (C3), 13.9 (C12).

(22)

Diethyl (2-bromoprop-2-en-1-yl)propanedioate – (22). This product was isolated as a clear oil in 52% yield (3.3 mmol scale, 474.5 mg) by method 3.2.1 with 2,3- dibromopropene as the alkyl halide; TLC (1:10 EtOAc:Hexanes), R_f = 0.36; ^1H NMR (CDCl_3 , 300 MHz) δ 5.68 (t, J = 1.0 Hz, 1H, H5), 5.47 (d, J = 2.0 Hz, 1H, H5), 4.21 (q, J = 7.0 Hz, 4H, H7), 3.78 (t, J = 7.5 Hz, 1H, H2), 3.02 (d, J = 3.0 Hz, 2H, H3), 1.28 (t, J = 7.0 Hz, 6H, H8); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.2 (C1), 129.4 (C4), 119.7 (C5), 61.7 (C7), 50.7 (C2), 40.4 (C3), 14.1 (C8).

(23)

Diethyl (2-bromoprop-2-en-1-yl)(methyl)propanedioate – (23). This product was isolated without purification as a crude brown oil in > 100% yield (15.0392 g) by method 3.2.2 with 2,3-dibromopropene as the alkyl halide; TLC (10% EtOAc:Hexanes), R_f = 0.52; ^1H NMR (CDCl_3 , 300 MHz) δ 5.66-5.64 (m, 1H, H5), 5.57 (d, J = 1.5, 1H, H5), 4.20 (q, J = 3.0 Hz, 4H, H8), 3.14 (d, J = 8.0 Hz, 2H, H3), 1.49 (s, 3H, H7), 1.27 (t, J = 7.0 Hz, 6H, H9).

Method 3.2.2 General Procedure for the Preparation of Diacids via Ester Hydrolysis.^{64b, 75, 76}

The appropriate alkylated diethylmalonate (1.0 eq.) was refluxed in a 1:1 mixture of [4N NaOH (4 eq) / MeOH] overnight. The reaction mixture, now containing the deprotonated product, was diluted with water ($\frac{1}{2}$ x original reaction volume) and extracted with diethyl ether ($\frac{1}{2}$ x original reaction volume). The organic layer was separated and the aqueous layer was acidified on ice with 6N HCl. The white precipitate that formed was extracted with DCM (3 x $\frac{1}{2}$ volume of aqueous precipitate mixture). The combined organic layers were dried on MgSO₄ and concentrated to yield the desired diacid, as a white solid, without further purification.

(2-bromobenzyl)propanedioic acid – (24). This product was isolated in 81% yield from the crude diester (22 g) by method 3.2.2; TLC (10% MeOH:EtOAc), $R_f = 0.3$; ¹H NMR (Acetone d₆, 400 MHz) δ 7.48-7.42 (m, 1H), 7.29-7.20 (m, 1H), 7.19-7.13 (m, 1H), 7.07-7.00 (m, 1H), 3.68 (t, $J = 8.0$ Hz, 1H, H2), 3.18 (d, $J = 6.0$ Hz, 2H, H3); ¹³C NMR (Acetone d₆, 100 MHz) δ 170.1 (C1), 138.5 (Ar), 133.7 (Ar), 133.6 (Ar), 129.6(Ar), 128.5 (Ar), 125.0 (Ar), 46.3 (C2), 35.6 (C3).

benzyl(methyl)propanedioic acid - (25). This product was isolated in 72% yield (53 mmol scale, 8 g) by method 3.2.2; TLC (1:5 MeOH:EtOAc), $R_f = 0.3$; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.28-7.10 (m, 4H, H5-9), 3.04 (s, 2H, H3), 1.32 (s, 3H, H10); ¹³C NMR (DMSO-d₆, 75 MHz) δ 173.1 (C1), 138.1(Ar), 137.3 (Ar), 136.0 (Ar), 124.2(Ar), 54.2 (C2), 20.0 (C3).

2-bromobenzyl(methyl)propanedioic acid – (26). This product was isolated in 92% yield (12.9 mmol scale, 3.40 g) by method 3.2.2; TLC (10% MeOH:EtOAc), $R_f = 0.36$; ¹H NMR (Acetone d₆, 400 MHz) δ 7.53-7.42 (m, 1H), 7.26-7.18 (m, 1H), 7.17-7.11 (m, 1H), 7.06-7.02 (m, 1H), 3.38 (s, 2H, H3), 1.14 (s, 3H, H10); ¹³C NMR (Acetone d₆, 100 MHz) δ 173.4 (C1), 137.7 (Ar), 133.8 (Ar), 132.3 (Ar), 129.5 (Ar), 128.4 (Ar), 126.8 (Ar), 55.1 (C2), 39.9 (C3), 19.6 (C10).

(2-bromoprop-2-en-1-yl)propanedioic acid – (27). This product was isolated in 35% yield (20.4 mmol scale, 1.7 g) by method 3.2.2; TLC (30% EtOAc:Hexanes), $R_f = 0.0$; ^1H NMR (Acetone d_6 , 300 MHz) δ 5.78-5.76 (m, 1H, H5), 5.49 (d, $J = 2.0$ Hz, 1H, H5), 3.73 (t, $J = 1.0$ Hz, 1H, H2), 3.00 (s, 2H, H3); ^{13}C (CDCl_3 , 100 MHz)

(2-bromoprop-2-en-1-yl)(methyl)propanedioic acid – (28). This product was isolated in 72% yield from the crude diester (46.4 mmol scale, 6.1 g) by method 3.2.2; TLC (30% EtOAc:Hexanes), $R_f = 0.0$; ^1H NMR (Acetone d_6 , 300 MHz) δ 5.80-5.78 (m, 1H, H5), 5.59-5.58 (m, 1H, H5), 3.14 (d, $J = 1.0$ Hz, 2H, H3), 1.47 (s, 3H, H7); ^{13}C NMR (Acetone d_6 , 75 MHz) δ 172.1 (C1), 128.2 (C4), 121.5 (C5), 52.8 (C2), 52.8 (C3), 46.0 (C2), 19.1 (C7).

Method 3.2.3 General Procedure for Malonamide Preparation.^{64a, 76-77}

The appropriate disubstituted malonic acid (1.0 eq.) and excess of thionyl chloride (0.3 M) were stirred at 60°C for ~ 4h. After removal of excess thionyl chloride in vacuo, the resulting dichloride was obtained as a yellow oil. It was then dissolved with DCM or chloroform (0.1 M) and split depending on how many different malonamides were required. On ice the appropriate amine (2.2 eq) was added and the solution was stirred at room temperature for 1h, triethylamine (2.2 eq.) was then added and the reaction mixture was stirred overnight at 60°C.

The crystalline products were isolated by re-crystallization from EtOAc while non-crystalline products were purified by chromatography on silica gel eluting with chloroform.

2-(2'-bromobenzyl)-2-methyl-malonamide – (29). The product was isolated as a white solid in 11% yield (4.8 mmol scale, 170 mg) by Method 3.2.3. TLC (30% EtOAc/Hexanes), $R_f = 0.0$; ^1H NMR (CDCl_3 , 400 MHz) δ 7.58-7.51 (m, 1H), 7.31-7.07 (m, 7H), 3.33 (s, 2H, H3), 1.12 (s, 3H, H10); HRMS (ESI-TOF) calculated for $\text{C}_{11}\text{H}_{14}\text{BrN}_2\text{O}_2$ ($M + H$)⁺ 285.0233; observed 285.0221.

(30)

2-(2'-bromobenzyl)-N,N',2-trimethylpropanediamide – (30). The product was isolated by recrystallization as a white solid in 51% yield (9.3 mmol scale, 1.480 g) by Method 3.2.3. mp = 131-134 °C; TLC (100% EtOAc), R_f = 0.18; ^1H NMR (CDCl_3 , 400 MHz) δ 7.54-7.45 (m, 1H), 7.21-7.01 (m, 2H), 7.08-6.90 (m, 3H), 3.40 (s, 2H, H3), 2.78 (d, 6H, H12, J = 5.0 Hz), 1.36 (s, 3H, H10); ^{13}C NMR (CDCl_3 , 100 MHz) δ 173.2 (C1), 136.5 (Ar), 133.0 (Ar), 131.1 (Ar), 128.4 (Ar), 127.3 (Ar), 126.0 (Ar), 54.4 (C2), 43.2 (C3), 26.7 (C12), 18.1 (C10); HRMS (ESI-TOF) calculated for $\text{C}_{13}\text{H}_{18}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 313.0546; observed 313.0542.

(31)

2-(2'-bromobenzyl)-N,N'-diisopropyl-2-methylpropanediamide – (31). The product was isolated by recrystallization as fine white solid needles in 36% yield (11.7 mmol scale, 1.65 g) by Method 3.2.3. mp = 168-171°C; TLC (30% EtOAc:Hexanes), R_f = 0.25; ^1H NMR (CDCl_3 , 400 MHz) δ 7.58-7.46 (m, 1H), 7.27-7.15 (m, 2H), 7.07-7.03 (m, 1H), 6.64 (d, J = 7.0 Hz, 2H, H11), 4.05 (dqq, J = 7.0 Hz, 6.5 Hz, 6.5 Hz, 2H, H12), 3.42 (s, 2H, H3), 1.34 (s, 3H, H10), 1.15 (d, J = 6.5 Hz, 6H, H13), 1.10 (d, J = 6.5 Hz, 6H, H14); ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.7 (C1), 136.7 (Ar), 133.0 (Ar), 131.1 (Ar), 128.4 (Ar), 127.3 (Ar), 126.1 (Ar),

54.2 (C2), 42.6 (C3), 41.8 (C12), 22.4 (C14), 22.3 (C13), 18.4 (C10); HRMS (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{26}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 369.1172; observed 369.1178.

(32)

2-(2'-bromobenzyl)-N,N'-di-n-butyl-2-methylpropanediamide – (32). This product was isolated by recrystallization as a white solid in 50% yield (11.7 mmol scale, 2.1547 g) by Method 3.2.3. mp = 135-138 °C; TLC (30% EtOAc:Hexanes), R_f = 0.26; ^1H NMR (CDCl_3 , 400 MHz) δ 7.59-7.47 (m, 1H), 7.24-7.13 (m, 2H), 7.08-7.02 (m, 1H), 6.87 (brt, J = 5.0 Hz, 2H, H11), 3.44 (s, 2H, H3), 3.28-3.23 (m, 2H, H12), 1.51-1.42 (m, 2H, H13), 1.37 (s, 3H, H10), 1.35-1.26 (m, 2H, H14), 0.91 (t, J = 7.5 Hz, 3H, H15); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.6 (C1), 136.6 (Ar), 133.0 (Ar), 131.0 (Ar), 128.4 (Ar), 127.3 (Ar), 126.0 (Ar), 54.4 (C2), 42.9 (C3), 39.7 (C12), 31.3 (C13), 20.0 (C14), 18.4 (C10), 13.7 (C15); HRMS (ESI-TOF) calculated for $\text{C}_{19}\text{H}_{30}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 397.1485; observed 397.1485.

(33)

2-(2'-bromobenzyl)-2-methyl-N,N'-diphenyl-malonamide – (33). This product was isolated by recrystallization as a white solid in 72% yield (3.9 mmol scale, 1.026 g) by Method 3.2.3. mp = 214-217 °C; TLC (30% EtOAc:Hexanes), R_f = 0.22; ^1H NMR (CDCl_3 , 400 MHz) δ 8.75 (s, 2H, H11), 7.59-7.55 (m, 1H), 7.53-

7.49 (m, 4H), 7.39-7.30 (m, 4H), 7.20-7.10 (m, 3H), 7.09-7.06 (m, 1H), 3.66 (s, 2H, H3), 1.64 (s, 3H, H10); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.7 (C1), 137.2 (Ar), 136.0 (Ar), 133.2 (Ar), 131.1 (Ar), 129.1 (Ar), 128.8 (Ar), 127.7 (Ar), 126.1 (Ar), 125.0 (Ar), 120.7 (Ar), 55.8 (C2), 43.6 (C3), 18.7 (C10); HRMS (EI-TOF) calculated for $\text{C}_{23}\text{H}_{21}\text{BrN}_2\text{O}_2$ (M^+) 436.0786; observed 436.0779.

***N,N'*-dibenzyl-2-(2-bromobenzyl)propanediamide – (34).** This product was isolated by recrystallization in 39% yield (38.2 mmol scale, 6.6388 g) by Method 3.2.3. TLC (30% EtOAc:Hexanes), R_f = 0.19; ^1H NMR (CDCl_3 , 400 MHz) δ 7.55-7.47 (m, 1H), 7.35-7.18 (m, 7H), 7.18-7.03 (m, 8H), 4.37 (d, J = 6.0 Hz, 4H, H11), 3.55 (t, J = 8.0 Hz, 1H, H2), 3.35 (d, J = 8.0 Hz, 2H, H3); ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.6 (C1), 137.6 (Ar), 136.9 (Ar), 133.0 (Ar), 131.5 (Ar), 128.7 (Ar), 128.6 (Ar), 127.6 (Ar), 127.5 (Ar), 127.5 (Ar), 124.3 (Ar), 54.5 (C2), 43.6 (C11), 38.7 (C3); HRMS (EI-TOF) calculated for $\text{C}_{24}\text{H}_{23}\text{BrN}_2\text{O}_2$ (M^+) 450.0943; observed 450.0936.

2-*N,N*-tribenzyl-2-methylpropanediamide – (35). This product was isolated by recrystallization as a white solid granules in 51% yield (10.8 mmol scale, 844 mg) by Method 3.2.3. mp = 155-158 °C; TLC (30% EtOAc:Hexanes), R_f = 0.29; ^1H

NMR (CDCl_3 , 400 MHz) δ 7.29-6.97 (m, 17 H, H5-9, H10, H13-17), 4.38-4.28 (m, 4H, H11), 3.14 (s, 2H, H3), 1.25 (s, 3H, H18); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.7 (C1), 137.8 (Ar), 136.3 (Ar), 130.1 (Ar), 128.7 (Ar), 128.3 (Ar), 127.6 (Ar), 127.5 (Ar), 127.0 (Ar), 54.4 (C2), 45.5 (C), 43.9 (C11), 18.1 (C10).

2-(2'-bromobenzyl)-*N,N'*-dibenzyl-2-methylpropanediamide-(36). This product was isolated by recrystallization as a white solid in 74% yield (3.9 mmol, 1.143 g) by Method 3.2.3. mp = 172-175 °C; TLC (30% EtOAc:Hexanes), R_f = 0.27; ^1H NMR (CDCl_3 , 400 MHz) δ 7.55-7.48 (m, 1H), 7.37-7.23 (m, 6H), 7.22-7.18 (m, 5H), 7.09-6.99 (m, 3H), 4.45-4.39 (m, 4H, H12), 3.50 (s, 2H, H3), 1.43 (s, 3H, H10); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.5 (C1), 137.7 (Ar), 136.3 (Ar), 133.1 (Ar), 131.1 (Ar), 128.7 (Ar), 128.5 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 126.0 (Ar), 54.6 (C1), 44.0 (C12), 43.0 (C3), 18.5 (C10); HRMS (EI-TOF) calculated for $\text{C}_{25}\text{H}_{25}\text{BrN}_2\text{O}_2$ (M^+) 464.1099; observed 464.1094.

2-(2'-bromobenzyl)-*N,N'*-bis(4-methoxybenzyl)-2-methylpropanediamide-37). This product was isolated by recrystallization as an off-white solid in 37% yield (3.9 mmol, 666 mg) by Method 3.2.3. mp = 148-151 °C; ^1H NMR (CDCl_3 ,

400 MHz) δ 7.54-7.49 (m, 1H), 7.16-7.02 (m, 9H), 6.89-6.77 (m, 4H), 4.40-4.36 (m, 4H, H12), 3.81 (s, 6H, H17), 3.49 (s, 2H, H3), 1.41 (s, 3H, H10); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.4 (C1), 159.1 (Ar), 136.4 (Ar), 133.0 (Ar), 131.1 (Ar), 129.8 (Ar), 129.1 (Ar), 128.4 (Ar), 127.6 (Ar), 126.0 (Ar), 114.1 (Ar), 55.3 (C17), 54.5 (C2), 43.5 (C12), 42.9 (C3), 18.4 (C10); HRMS (EI-TOF) calculated for $\text{C}_{27}\text{H}_{29}\text{BrN}_2\text{O}_4$ (M^+) 524.1311; observed 524.1296.

2-(2'-bromobenzyl)-2-methyl-N,N'-bis(2,6-dimethylphenyl)propanediamide – (38). This product was isolated by recrystallization as a white solid in 16% yield (9.3 mmol, 740 mg) by Method 3.2.3. mp = 196-199 °C; TLC (40% EtOAc:Hexanes), R_f = 0.46; ^1H NMR (CDCl_3 , 400 MHz) δ 8.40 (s, 2H, H11), 7.64-7.58 (m, 1H), 7.48-7.43 (m, 1H), 7.24-7.20 (m, 1H), 7.15-7.04 (m, 7H), 3.81 (s, 2H, H3), 2.13 (s, 12H, H18-19), 1.81 (s, 3H, H10); ^{13}C (CDCl_3 , 100 MHz) δ 171.1 (C1), 136.4 (Ar), 135.0 (Ar), 133.5 (Ar), 133.3 (Ar), 131.2 (Ar), 128.7 (Ar), 128.3 (Ar), 127.8 (Ar), 127.4 (Ar), 55.3 (C2), 42.6 (C3), 21.3 (C10), 18.5 (C18); HRMS (EI-TOF) calculated for $\text{C}_{27}\text{H}_{29}\text{BrN}_2\text{O}_2$ (M^+) 492.1412; observed 492.1405.

2-(2'-bromobenzyl)-N,N'-bis-1-aminonaphthalene-2-methyl-malonamide – (39). This product was isolated by recrystallization as a white solid in 30% yield (9.3 mmol, 1.515 g) by Method 3.2.3. mp = 185-187 °C; TLC (0.4-1.0 EtOAc:Hexanes), R_f = 0.42; ^1H NMR (CDCl_3 , 400 MHz) δ 9.34 (s, 2H, H11), 8.01 (d, J = 7.5 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 4H), 7.64 (d, J = 8.0 Hz, 1H), 7.55-7.34 (m, 7H), 7.27-7.07 (m, 2H), 3.78 (s, 2H, H3), 1.83 (s, 3H, H10); ^{13}C (CDCl_3 , 100 MHz) δ 171.6 (C1), 136.0 (Ar), 134.2 (Ar), 133.3 (Ar), 132.0 (Ar), 131.3 (Ar), 128.9 (Ar), 128.7 (Ar), 127.8 (Ar), 127.3 (Ar), 126.6 (Ar), 126.3 (Ar), 126.2 (Ar), 125.7 (Ar), 120.9 (Ar), 120.7 (Ar), 56.1 (C2), 44.0 (C3), 19.3 (C10); HRMS (EI-TOF) calculated for $\text{C}_{31}\text{H}_{25}\text{BrN}_2\text{O}_2$ (M^+) 536.1086; observed 536.1086.

2-(2-bromobenzyl)-N,N'-di-tert-butylpropanediamide – (40). This product was isolated by column chromatography in 16% yield (18.5 mmol scale, 1.342 g) by method 3.2.3. TLC (50% DCM:Hexanes), R_f = 0.2; ^1H NMR (CDCl_3 , 400 MHz) δ 7.59-7.45 (m, 1H), 7.26-7.13 (m, 2H), 7.11-7.00 (m, 1H), 6.67 (brs, 1H, H10), 3.28-3.22 (m, 3H, H2 & H3), 1.26-1.15 (m, 18H, H12-14); ^{13}C (CDCl_3 , 75 MHz) δ 169.5 (C1), 137.4 (Ar), 132.9 (Ar), 131.7 (Ar), 128.5 (Ar), 127.3 (Ar), 124.4 (Ar), 55.7 (C2), 51.2, 39.2, 28.5. HRMS (ESI-TOF) calculated for $\text{C}_{18}\text{H}_{28}\text{BrN}_2\text{O}_2$ ($\text{M} + \text{H}^+$) 383.1328; observed 383.1320.

2-(2-bromoprop-2-en-1-yl)-N,N'-di-tert-butylpropanediamide-(41). This product was isolated by column chromatography as a white solid in 17% yield (1.8 mmol scale, 100 mg) by Method 3.2.3. mp = 131-134 °C; TLC (30% EtOAc:Hexanes), R_f = 0.7; ^1H NMR (CDCl_3 , 400 MHz) δ 6.90 (brs, 2H, H6), 5.65-5.64 (m, 1H, H5a), 5.43 (d, J = 1.5 Hz, 1H, H5b), 3.20 (td, J = 10.5 Hz, J = 1.5 Hz, 1H, H2), 2.86 (d, J = 7.5 Hz, 2H, H3), 1.31 (s, 18H, H8-10); ^{13}C (CDCl_3 , 75 MHz) δ 169.2 (C1), 130.1 (C5), 119.7 (C4), 54.6 (C2), 51.6 (C7), 44.5 (C3), 28.7 (C8); HRMS (ESI-TOF) calculated for $\text{C}_{14}\text{H}_{25}\text{BrN}_2\text{O}_2$ ($M + \text{H}$) $^+$ 333.1172; observed 333.1181.

N,N'-dibenzyl-2-(2-bromoprop-2-en-1-yl)propanediamide – (42). This product was isolated in 14% yield (7.4 mmol scale, 425.5 mg) by Method 3.2.3. TLC (10% EtOAc:Hexanes), R_f = 0.5; ^1H NMR (CDCl_3 , 400 MHz) δ 7.18-6.95 (m, 10H), 6.89 (bs, 2H), 5.42 (s, 1H, H5a), 5.20 (d, J = 2.0 Hz, 1H, H5b), 4.20 (d, J = 6.0 Hz, 4H, H7), 3.29 (t, J = 7.5 Hz, 1H, H2), 2.77 (d, J = 7.5 Hz, 2H, H3); HRMS (ESI-TOF) calculated for $\text{C}_{20}\text{H}_{22}\text{BrN}_2\text{O}_2$ ($M + \text{H}$) $^+$ 401.0859; observed 401.0868.

2-(2-bromoprop-2-en-1-yl)-2-methylpropanedioic acid, t-butyl monoamide - (43). This product was isolated by column chromatography in 12% yield (30.58 mmol scale, 1.061 g) by Method 3.2.3. TLC (20% EtOAc:Hexanes), R_f = 0.19; ^1H NMR (CDCl_3 , 400 MHz) δ 8.75 (brs, 1H, H7), 6.60 (s, 1H, H9), 5.59-5.58 (m, 1H, H5), 5.49 (d, J = 2.0 Hz, 1H, H5), 3.14 (d, J = 15.0 Hz, 1H, H3a), 2.96 (d, J = 15.0 Hz, 1H, H3b), 1.95 (s, 3H, H6), 1.34 (s, 9H, H11); ^{13}C (CDCl_3 , 100 MHz) δ 176.2 (C1), 171.6 (C8), 127.3 (C4), 121.1 (C5), 52.4 (C2), 52.2 (C10), 48.1 (C3), 28.4 (C11), 22.3 (C6). HRMS (ESI-TOF) calculated for $\text{C}_{11}\text{H}_{19}\text{BrNO}_3$ ($M + \text{H}$) $^+$ 292.0542; observed 292.0542.

N,N'-dibenzyl-2-(2-bromoprop-2-en-1-yl)-2-methylpropanediamide-(44). This product was isolated in 77% yield (4.37 mmol scale, 800 mg) by Method 3.2.3. TLC (100% DCM), R_f = 0.3; ^1H NMR (CDCl_3 , 400 MHz) δ 7.26-7.10 (m, 10H, H10-14), 5.52 (s, 1H, H5a), 5.44 (d, J = 1.5 Hz, 1H, H5b), 4.41-4.28 (m, 4H, H8), 3.05 (s, 2H, H3), 1.43 (s, 3H, H6); ^{13}C (CDCl_3 , 100 MHz) δ 171.2 (C1), 137.7 (Ar), 128.7 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 121.6 (C5), 52.8 (C2), 49.0 (C3), 44.1 (C8), 18.5 (C6). HRMS (ESI-TOF) calculated for $\text{C}_{21}\text{H}_{24}\text{BrN}_2\text{O}_2$ ($M + \text{H}$) $^+$ 415.1015; observed 415.1023.

3.3 General Procedure for Malonamide Reduction

Method 3.3.1

LiAlH_4 (6 eq.) was carefully added to an evacuated and backfilled round bottom flask containing benzylmalonamide (36), (1.0eq.) dissolved in THF (0.1M). The mixture was refluxed over night, cooled to room temperature and quenched with 1:1:3 H_2O :15%NaOH:THF, filtered through celite and extracted against DCM. The

combined organic layers were dried on MgSO_4 and concentrated to yield a yellow oil, without further purification.

(45)

2-(2'-bromobenzyl)-N,N'-dibenzyl-2-methylpropanediamine-(45). This product was isolated as a white solid in 80% yield (1 mmol scale, 375 mg) by Method 3.3.1. mp = 131-134 °C; TLC (EtOAc), R_f = 0.18; ^1H NMR (DMSO-d_6 , 300 MHz) δ 7.32-7.03 (m, 16H), 3.63 (s, 4H), 2.54 (s, 2H), 2.26-2.23 (m, 3H), 0.70 (s, 2H).

3.4 General Procedure for the Intramolecular Malonamide Cyclization

Method 3.4.1 Sealed Tube

A dry 10 mL Schlenk tube with a glass stopper was charged with $\text{Pd}(\text{OAc})_2$ (3.3 mol %), (*R*)-MOP (6.6 mol %), and the appropriate solid malonamide (1.0 eq.). The reaction vessel was evacuated and backfilled in between the addition of each solid. Anhydrous toluene (0.1 M) was added under a stream of nitrogen and the sealed mixture was heated at 100°C to dissolve the solids (3 min). The reaction vessel was removed from the oil bath temporarily and charged with Cs_2CO_3 (1.4 eq.) under a stream of nitrogen, capped, sealed with teflon tape and stirred over night at 100 °C (~ 24 h). The reaction mixture was cooled to room temperature, diluted with DCM or EtOAc (3 X original volume), filtered through a short plug of celite washing with the same solvent and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel eluting with 30-100 % EtOAc:Hexanes or 100 % DCM.³³ The enantiomeric excesses were determined with HPLC on a CHIRALCEL OD-H column 125 cm x 0.46 cm i.d. eluting with *i*-PrOH in hexanes with a flow rate of 0.65 mL/min at 256 nm.

Method 3.4.2 Under Reflux with Palladium

A dry 10 or 25mL round bottom flask equipped with a reflux condenser with a connection a to a stream of nitrogen through a connection from the top of the condenser to a double manifold was charged with $\text{Pd}(\text{OAc})_2$ (3.3 mol %), (*R*)-MOP (6.6 mol %), and the appropriate solid malonamide (scale based on 100 mg of cyclic product). The reaction vessel was evacuated and backfilled in between the addition of each solid. Anhydrous THF (0.05 M) was added under a stream of nitrogen and the sealed mixture was heated at 80°C to dissolve the solids. The reaction vessel was removed from the oil, cooled and charged with the appropriate base (Cs_2CO_3 or K_3PO_4), capped, sealed with teflon tape and stirred over night in refluxing THF ~80 °C (~ 24 h). The reaction mixture was cooled to room temperature, diluted with DCM or EtOAc (3 X original volume), filtered through a short plug of celite washing with the same solvent and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel eluting with 30-100 % EtOAc:Hexanes or 100 % DCM.

Method 3.4.3 Under Reflux with Copper

A dry 5 or 10 mL round bottom flask equipped with a reflux condenser with a connection to a stream of nitrogen through a connection from the top of the condenser to a double manifold was charged with CuI (10 mol %), Ligand (20 mol %), and the appropriate solid malonamide (scale based on 100 mg of cyclic product). The reaction vessel was evacuated and backfilled in between the addition of each solid. Anhydrous THF (0.05 M) was added under a stream of nitrogen and the sealed mixture was heated at 80°C to dissolve the solids. The reaction vessel was removed from the oil, cooled and charged with the appropriate base (Cs_2CO_3 or K_3PO_4), capped, sealed with teflon tape and stirred over night in refluxing THF ~80 °C (~ 24 h). The reaction mixture was cooled to room temperature, diluted with DCM or EtOAc (3 X original volume), filtered through a short plug of celite washing with the same solvent and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel eluting with 30-100% EtOAc:Hexanes or 100 % DCM.²³ The enantiomeric

excesses were determined with HPLC on a CHIRALCEL OD-H column 125 cm x 0.46 cm i.d. eluting with 10% *i*-PrOH in hexanes with a flow rate of 0.65 mL/min at 236 nm.

***N*,1,3-trimethyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide - (46).** This product was isolated as a white semi-solid in 101% yield (101 mg) by method 3.4.2 employing Cs_2CO_3 as the base. mp = 126-129 °C; TLC (100% EtOAc), R_f =; 0.31; ^1H NMR (CDCl_3 , 400 MHz) δ 7.27-7.22 (m, 2H), 7.13 (brs, 1H), 7.06-7.02 (m, 1H), 6.96-6.92 (m, 1H), 3.37-3.27 (m, 1H, H4, and a singlet underneath for 3H, H9), 2.88 (d, J = 15.5 Hz, 1H, H4ii), 2.66 (d, J = 5.0 Hz, 3H, H13), 1.37 (s, 3H, H10); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.7 (C11), 171.6 (C2), 138.9 (C4a), 128.7 (Ar), 127.5 (Ar), 124.6 (Ar), 123.8 (Ar), 114.3 (C8a), 48.3 (C3), 35.2 (C4), 30.4 (C9), 26.5 (C13), 23.5 (C10); HRMS (ESI-TOF) calculated for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 233.1284; observed 233.1296.; HPLC eluting with 1% *i*-PrOH : hexanes; t_R major = 17.9 min, t_R minor = 25.6 min; 38% ee.

***N*,1-diisopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide - (47).** This product was isolated as a white solid in 90% yield (90.7 mg) by method 3.4.2 employing K_3PO_4 as the base. mp = 115-118 °C; TLC (40%

EtOAc:Hexanes), R_f = 0.2; ^1H NMR (CDCl_3 , 400 MHz) δ 7.32-7.18 (m, 2H), 7.08-6.94 (m, 2H), 6.41 (d, J = 6.5 Hz, 1H, H14), 4.63 (septet, J = 7.0 Hz, 1H, H9) 3.89 (dseptets, J = 7.0 Hz, J = 6.5 Hz, 1H, H15), 3.31 (d, J = 15.5 Hz, 1H, H4a), 2.83 (d, J = 15.5 Hz, 1H, H4b), 1.55 (q, J = 6.0 Hz, 6H, H10-11), 1.43 (s, 3H, H12), 1.07 (d, J = 6.5 Hz, 3H, H16), 0.92 (d, J = 6.5 Hz, 3H, H17); ^{13}C NMR (CDCl_3 , 100 MHz) δ 173.1 (C2), 169.8 (C13), 138.6 (C4a), 128.9 (Ar), 127.1 (Ar), 126.8 (Ar), 126.6 (Ar), 115.4 (Ar), 49.8 (C9), 49.3 (C3), 41.2 (C15), 35.4 (C4), 22.8 (C12), 22.5 (C16), 22.3 (C17), 20.3 (C11), 19.3 (C10); HRMS (ESI-TOF) calculated for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 289.191; observed 289.1905; HPLC eluting with 1% *i*-PrOH : hexanes; eluting with 1% *i*-Pr : hexanes; t_R major = 21.0 min, t_R minor = 25.4 min; 70% ee.

***N*,1-dibutyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide-(48).**

This product was isolated as a pale orange glass in 103 % yield (103 mg) by method 3.4.2 employing Cs_2CO_3 as the base. TLC (0.4:1.0 EtOAc:Hexanes), R_f = 0.23; ^1H NMR (CDCl_3 , 400 MHz) δ 7.22-7.10 (m, 2H), 6.99-6.92 (m, 1H), 6.87-6.80 (m, 2H), 3.89-3.82 (m, 2H, H9), 3.30 (d, J = 15.5 Hz, 1H, H4i), 3.11-3.05 (m, 2H, H16), 2.84 (d, J = 15.5 Hz, 1H, H4ii), 1.61-1.53 (m, 2H, H10), 1.38 (s, 3H, H13), 1.34-1.27 (m, 4H, H11, H17), 1.18-1.13 (m, 2H, H18), 0.91 (t, J = 7.5 Hz, 3H, H12), 0.78 (t, J = 7.5 Hz, 3H, H19); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.2 (C2), 170.9 (C14), 138.0 (C4a), 128.9 (Ar), 127.4 (Ar), 125.0 (Ar), 123.6 (Ar), 114.3 (8a), 48.3 (alkyl), 43.0 (alkyl), 39.2 (alkyl), 35.3 (alkyl), 31.4 (alkyl), 29.0 (alkyl), 23.2 (alkyl), 20.2 (alkyl), 19.9 (alkyl), 13.8 (alkyl), 13.7 (alkyl); HRMS (EI-TOF) calculated for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2$ (M) $^+$ 316.2151; observed 316.2151; HPLC eluting with 1% *i*-PrOH : hexanes; t_R major = 14.2 min, t_R minor = 20.9 min; 54% ee.

(49)

3-methyl-2-oxo-N,1-diphenyl-1,2,3,4-tetrahydroquinoline-3-carboxamide-

(49). This product was isolated as a white solid in 99% yield (997 mg) by method 3.4.2 employing Cs_2CO_3 as the base. Mp = 156-159 °C. TLC (40% EtOAc:Hexanes), R_f = 0.29 ^1H NMR (CDCl_3 , 400 MHz) δ 9.92 (s, 1H, H17), 7.62-7.44 (m, 5H), 7.37-7.19 (m, 6H), 7.10-6.99 (m, 3H), 3.47 (d, J = 16.0 Hz, 1H, H4i), 3.22 (d, J = 16.0 Hz, 1H, H4ii), 1.55 (s, 3H, H15); ^{13}C NMR (CDCl_3 , 100 MHz) δ 173.2 (C2), 169.4 (C16), 139.8 (Ar), 138.0 (Ar), 137.9 (Ar), 130.2 (Ar), 129.0 (Ar), 128.9 (Ar), 128.8 (Ar), 128.7 (Ar), 127.3 (Ar), 124.7 (Ar), 124.1 (Ar), 123.5 (Ar), 120.1 (Ar), 116.5 (Ar), 48.1 (C3), 35.0 (C4), 23.3 (C15); HRMS (ESI-TOF) calculated for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 357.1594; observed 357.1607; HPLC eluting with 10% *i*-PrOH : hexanes; t_R major = 15.3 min, t_R minor = 16.7 min; 58% ee.

(50)

N,1-dibenzyl-3-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide-

(50). This product was isolated as an off-white solid in 100 % yield (100 mg) by method 3.4.2 employing Cs_2CO_3 as the base. mp = 135-138 °C; TLC (30% EtOAc:Hexanes), R_f = 0.95; ^1H NMR (400 MHz, CDCl_3), 7.29-6.95 (m, 15H), 6.77 (d, J = 7.5 Hz, 1H), 5.14-5.00 (m, 2H, H9), 4.38 (d, J = 6.0 Hz, 2H, H19), 3.43 (d, J = 15.5 Hz, 1H, H4i), 2.99 (d, J = 15.5 Hz 1H, 1H, H4ii), 1.49 (s, 3H, H16); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.4 (C2), 171.0 (C17), 138.6 (Ar), 138.0 (Ar), 136.5, (Ar), 128.9, (Ar), 128.8, (Ar), 128.6, (Ar), 127.6, (Ar), 127.5, (Ar), 127.3, (Ar), 127.2, (Ar), 126.0, (Ar), 124.7, (Ar), 123.9, (Ar), 115.3 (Ar), 48.7 (C3), 47.4 (C9), 43.6 (C19), 35.5 (C4), 23.3 (C16); HRMS (ESI-TOF) calculated for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_2$ ($M + H$) $^+$ 385.191; observed 385.1903; HPLC eluting with 20% *i*-PrOH : hexanes; t_R major = 23.8 min, t_R minor = 18.06 min; (57% ee).

(51)

3-methyl-N,1-bis(4-methoxybenzyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-

carboxamide – (51). This product was isolated as a white solid in 99% yield (99 mg) by method 3.4.2 employing Cs_2CO_3 as the base. mp = 119-122 °C; TLC (70% EtOAc:Hexanes), R_f = 0.63; ^1H NMR (CDCl_3 , 400 MHz) δ 7.22-7.15 (m, 1H), 7.11-7.02 (m, 2H), 7.00-6.89 (m, 5H), 6.80 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 5.07 (d, J = 16.0 Hz, 1H, H9i), 4.91 (d, J = 16.0 Hz, 1H, H9ii), 4.23-4.12 (m, 2H, H20), 3.69 (s, 3H, H14), 3.67 (s, 3H, H25), 3.42 (d, J = 15.5 Hz, 1H, H4i), 2.95 (d, J = 15.5, 1H, H4ii), 1.47 (s, 3H, H17); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.3 (C2), 170.8 (C18), 159.0 (Ar), 158.7 (Ar), 138.7 (Ar), 130.2 (Ar), 129.0 (Ar), 128.8 (Ar), 128.5 (Ar), 127.5 (Ar), 127.3 (Ar), 124.8 (Ar), 123.9 (Ar), 115.3 (Ar), 114.2 (Ar), 114.0 (Ar), 55.3 (C14), 55.2 (C25), 48.7 (C3), 46.8 (C9), 43.1 (C20), 35.8 (C4), 14.2 (C17); HRMS (EI-TOF) calculated for

$C_{27}H_{28}N_2O_4$ (M^+) 444.2049; observed 444.2050 ; HPLC eluting with 20% *i*-PrOH : hexanes; t_R major = 36.4, t_R minor = 31.2 min; 75% ee.

(52)

3-methyl-*N*,1-bis(2,6-dimethylphenyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxamide – (52). This product was isolated by method 3.4.2 with K_3PO_4 as a mixture with starting material (**38**) in a mole ratio (determined by NMR) of 0.732:1 (**38**:**52**). Mass ratio = 0.88:1 (**38**:**52**). Of the 103 mg white solid isolated, approximately 53% was **52**, representing approximately a 54% yield. mp = 82-85 °C; TLC (0.3:1 EtOAc:Hexanes), R_f = 0.46; 1H NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H, H19), 7.27-7.12 (m, 4H), 7.03-6.95 (m, 5 H), 6.18-6.14 (m, 1H), 3.46 (d, J = 16.0 Hz, 1H), 3.29 (d, J = 16.0 Hz, 1H), 2.09-1.97 (singlets, not differentiated from signals due to **38**), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9 (C2), 171.1 (C13), 138.0 (Ar), 136.2 (Ar), 135.9 (Ar), 135.6 (Ar), 134.9 (Ar), 134.0 (Ar), 130.6 (Ar), 129.2 (Ar), 128.9 (Ar), 128.5 (Ar), 128.1(Ar), 127.2(Ar), 126.8(Ar), 124.1(Ar), 115.1(Ar), 55.5 (C3), 35.7 (C4), 19.2 (C15), 18.5 (C19), 18.4 (C21), 17.7 (C27), 17.5 (C17); HRMS (ESI-TOF) calculated for $C_{27}H_{29}N_2O_2$ (M^+) 444.2049; observed 444.2050; HPLC eluting with 8% *i*-PrOH : hexanes; t_R major = 13.3 , t_R minor = 16.9 min. Enantiomeric excess not determined due to uncertainty of compound identities in chromatogram (**38** vs. **52**).

(53)

3-methyl-*N*,1-bis(1-naphthyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-

carboxamide – (53). This product was isolated as an inseparable mixture of isomers, pale orange solid in 79% yield (79 mg) by method 3.4.2 employing K_3PO_4 as the base. mp = 198-201 °C; TLC (DCM), R_f = 0.24; 1H NMR ($CDCl_3$, 400 MHz) δ 10.6 (s, 0.5H), 10.14 (s, 0.7H), 8.23-7.26 (m, 12.3H), 7.21-6.92 (m, 2.6H), 6.17-6.15 (m, 1H), 3.85 (d, J = 16.0 Hz, 0.7H), 3.77 (d, J = 16.0 Hz, 0.4H), 3.54 (d, J = 16.0 Hz, 0.4H) 3.47 (d, J = 16.0 Hz, 0.7H), 1.91 (s, 1H), 1.87 (s, 1.5H), 1.55 (s, 3H), 1.27 (s,); HRMS (ES-TOF) calculated for $C_{31}H_{24}N_2O_2$ (M^+) 456.1836; observed 456.1840; HPLC eluting with 17% *i*-PrOH: hexanes three peaks were observed: t_R major = 36.0 min, t_R minor = 29.1 min, t_R minor = 40.3 min; ee couldn't be determined. The sample doesn't show any obvious impurity in the EI spectrum, the impurity seen with HPLC is an inseparable mixture of diastereomers (see **Figure 13**, p.42).

***N*,1-dibenzyl-3-methyl-5-methylidene-2-oxopyrrolidine-3-carboxamide - (54).**

This product was isolated with L-Pro as the ligand as a yellow oil that solidified, in 87 % yield (23.7 mg) by method 3.4.3. mp = n.d; TLC (40% EtOAc:Hexanes), R_f = 0.36; ^1H NMR (CDCl_3 , 400 MHz) δ 7.79 (t, J = 2.0 Hz, 1H, H16), 7.37-7.22 (m, 9H), 7.20-7.10 (m, 2H), 4.68 (d, J = 3.0 Hz, 2H, H7), 4.56-4.39 (m, 2H, H17), 4.31-4.25 (m, 2H, H6), 3.50 (dt, J = 17.0 Hz, J = 2.0 Hz, 1H, H4a), 2.61 (dt, J = 17.0 Hz, J = 1.50 Hz, 1H, H4b), 1.61 (s, 3H, H14); ^{13}C NMR (CDCl_3 , 100 MHz) δ 177.4, 171.0, 142.6, 138.1, 135.5, 128.74, 128.70, 127.6, 127.5, 127.4, 127.0 (Ar), 87.7, 50.1, 44.1, 43.6, 25.7, 14.2; HRMS (ESI-TOF) calculated for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 335.1754; observed 335.1770; HPLC eluting with 16% *i*-PrOH : hexanes three peaks were observed: t_R major = 36.0 min, t_R minor = 29.1 min, t_R minor = 40.3 min; ee couldn't be determined as both enantiomer eluted together.

***N*,1-dibenzyl-2-oxo-1,2-dihydroquinoline-3-carboxamide - (55).** This product was isolated as a yellow oil that solidified, in 77 % yield (28.4 mg) by method 3.4.1 employing Cs_2CO_3 as the base. mp = n.d; TLC (30% EtOAc:Hexanes), R_f = 0.36; ^1H NMR (400 MHz, D_2O), 10.4 (bt, 1H, H18), 9.01 (s, 1H, H4), 7.84-7.72 (m, 1H), 7.60-7.47 (m, 1H), 7.37-6.91 (m, 14H), 5.60 (s, 2H, H9), 4.68 (d, 2H, H19); HRMS (ESI-TOF) calculated for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$ 369.1597; observed 369.11612.

4 CONCLUSION:

As a preliminary literature example, a new approach to enantioselective synthesis with nitrogen nucleophiles (the Buchwald-Hartwig coupling) has been developed through the desymmetrization of prochiral dinitrogen malonamide derivatives via an enantioselective intramolecular arylation. Various reaction conditions were screened and with the optimized reaction conditions consisting of a 1:2 ratio of $\text{Pd}(\text{OAc})_2$ (3.3 mol %) / (*R*)-MOP (6.6 mol %) with Cs_2CO_3 or K_3PO_4 in refluxing THF afforded the best results with the 4-methoxybenzyl substituted malonamide in >99% yield and 75% yield. This enantioselective methodology can be pursued further to synthesize novel biologically active quinolinones. The monophosphine ligands (*R*)-MOP gave the highest enantioselectivities in comparison to the different types of ligands screened. In contrast to axially chiral bisphosphine ligands, the versatile coordination ability of MOP allows the ligand to monocoordinate palladium leaving an open coordination site believed to be the difference in the much higher enantioselectivities observed. The enantioselective intermolecular N-arylation reaction was attempted but failed to give either a clean reaction or any characterizable products by NMR. A mild Goldberg reaction with enantiopure copper ligands produced the target 5-membered vinyl ring from a bromovinyl malonamide precursor with up to 87% yield and undetermined enantioselectivities employing either Chiralcel OD-H or Chiralpak AD-H column.

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6.0 APPENDIX: NMR spectra (¹H, ¹³C) and HPLC chromatograms

Virre/Ryerson
A56
May 7 2007

PROTON128 CDC13 D:\\ Lukas 1

C13CPD CDC13 D:\\ Lukas 1

Virre/Ryerson
a59(10)
May 7 2007

Virre/Ryerson
a59(12)
May 7 2007

Ryerson
lpb18_6_11

Vitre/Eyerson
LPA64

C13CPD Acetone D:\ Lukas 1

LPA32

PROTON Acetone D:\\ Lukas 1

C13CPD Acetone D:\\ Lukas 1

RYE LP B-27, TUBE 4

RYE LP B-27, TUBE 4

LPB9

LPB9
Tube2
C13
(50)

Viirre/Ryerson
A55
may 7 2007

PROTON CDCl3 D:\ Lukas 1

C13CPD CDC13 D:\ Lukas 1

PROTON CDCl3 D:\\ Lukas 1

C13CPD32 CDCl3 D:\\ Lukas 1

PROTON CDC13 D:\\ Lukas 1

C13CPD CDC13 D:\\ Lukas 1

PROTON CDCl3 D:\\ Lukas 1

C13CPD CDCl3 D:\\ Lukas 1

C13CPD CDCl3 D:\ Lukas 1

(35)

inter
C13CPD32 CDCl3 D:\\ Lukas 1

PROTON CDCl3 D:\\ Luka

C13CPD32 CDCl3 D:\\ Lukas 1

PROTON128 CDCl3 D:\\ Lukas 1

C13CPD32 CDC13 D:\ Lukas 1

PROTON CDC13 D:\ Lukas 1

C13CPD CDC13 D:\\ Lukas 1

PROTON CDC13 D:\\ Luka:

C13CPD CDCl3 D:\\ Lukas 1

PROTON CDCl3 D:\\ Lukas 1

RYE_LPB28_1_2

RYE_LPB28_1_2

bn or t-bu? check
C13CPD32 CDCl3 D:\ Lukas 1

Chromatogram

Sample Name : C6 MeQ
 File Name : \\Poweredge\E drive\TC\dennis\LP049-20080703-144613.raw
 Date : 7/3/08 1:51:56 PM
 Method : C6 MeQ
 Start Time : 0.00 min
 End Time : 29.99 min
 Scale Factor : 1.0
 Time of Injection : 7/3/08 2:45:59 PM
 Low Point : -31.68 mV
 High Point : 623.56 mV
 Plot Scale : 665.3 mV

Software Version : 6.1.2.0.1:D19
 Operator : manager
 Sample Number : 13%IPA tst
 AutoSampler : SER200
 Instrument Name : LC
 Instrument Serial # : None
 Delay Time : 0.00 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul
 Sample Amount : 1.0000
 Data Acquisition Time : 7/3/08 2:45:59 PM
 Date : 7/3/08 1:51:56 PM
 Sample Name : C6 MeQ
 Study :
 Rack/Vial : 0/2
 Channel : B
 A/D mV Range : 1000
 End Time : 29.99 min
 Area Reject : 0.000000
 Dilution Factor : 1.00
 Cycle : 211

Raw Data File : \\Poweredge\E drive\TC\dennis\LP049-20080703-144613.raw
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 Proc Method : \\Poweredge\E drive\TC\dennis\Cpak ADH
 Calib Method : \\Poweredge\E drive\TC\dennis\Cpak ADH
 Sequence File : \\Poweredge\E drive\TC\dennis\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	4.553	311387.40	24962.71	0.97	0.97	BB	12.4741
2	11.332	164821.60	1009.72	0.51	0.51	BB	163.2342
3	17.870	21861027.60	626879.83	68.19	68.19	BB	34.8728
4	25.482	9720735.40	181939.79	30.32	30.32	BB	53.4283
		32057972.00	834792.06	100.00	100.00		

PROTON128 CDC13 D:\\ Lukas 1

Chromatogram

Sample Name: B97 iPrQ
 File Name: \\Poweredge\E drive\TC\dennis\LP049-20080708-145603.raw
 Date: 7/8/08 2:01:32 PM
 Method: Cpak ADH from \\Poweredge\E drive\TC\dennis\LP049-20080708-140132.rst
 Start Time: 0.00 min
 End Time: 29.99 min
 Scale Factor: 1.0
 Time of Injection: 7/8/08 2:55:43 PM
 Low Point: -7.67 mV
 High Point: 255.61 mV
 Pot Offset: 7.67 mV
 Pot Scale: 263.3 mV

Software Version : 6.1.2.0.1:D19
 Operator : manager
 Sample Number : 1%IPA tst
 AutoSampler : SER200
 Instrument Name : LC
 Instrument Serial # : None
 Delay Time : 0.00 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul
 Sample Amount : 1.0000
 Data Acquisition Time : 7/8/08 2:55:43 PM
 Date : 7/8/08 2:01:32 PM
 Sample Name : B97 iPrQ
 Study :
 Rack/Vial : 0/2
 Channel : B
 A/D mV Range : 1000
 End Time : 29.99 min
 Area Reject : 0.000000
 Dilution Factor : 1.00
 Cycle : 227

Raw Data File : \\Poweredge\E drive\TC\dennis\LP049-20080708-145603.raw
 Result File : \\Poweredge\E drive\TC\dennis\LP049-20080708-140132.rst
 Inst Method : \\poweredge\E drive\TC\dennis\Cpak ADH from \\Poweredge\E drive\TC\dennis\LP049-20080708-140132.rst
 Proc Method : \\Poweredge\E drive\TC\dennis\Cpak ADH
 Calib Method : \\Poweredge\E drive\TC\dennis\Cpak ADH
 Sequence File : \\poweredge\E drive\TC\dennis\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	5.504	28341.60	3277.28	0.18	0.18	BB	8.6479
2	5.870	47432.00	4548.29	0.31	0.31	BB	10.4285
3	20.995	12978240.00	248987.34	84.14	84.14	BB	52.1241
4	25.370	2369845.20	38238.29	15.36	15.36	BB	61.9757
		15423858.80	295051.19	100.00	100.00		

PROTON128 CDCl3 D:\ Lukas 1

C13CPD CDCl3 D:\ Lukas 1

Chromatogram

Sample Name : B69 BuQ 3% IPA
 File Name : \\Poweredge\\E drive\\TC\\dennis\\LP019-20080503-120610.raw
 Date : 5/3/08 11:18:08 AM
 Method : GCADH-120610
 Start Time : 0.00 min
 Scale Factor : 1.0
 Time of Injection : 5/3/08 12:05:57 PM
 Low Point : 14.12 min
 High Point : 27.04 min
 End Time : 29.99 min
 Pot Offset : 10.23 min

Software Version : 6.1.2.0.1:D19
 Operator : manager
 Sample Number : CCOD-H-30ul
 AutoSampler : SER200
 Instrument Name : LC
 Instrument Serial # : None
 Delay Time : 0.00 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul
 Sample Amount : 1.0000
 Data Acquisition Time : 5/3/08 12:05:57 PM
 Date : 5/3/08 11:18:08 AM
 Sample Name : B69 BuQ 3% IPA
 Study : chirals
 Rack/Vial : 0/1
 Channel : B
 A/D mV Range : 1000
 End Time : 29.99 min
 Area Reject : 0.000000
 Dilution Factor : 1.00
 Cycle : 102

Raw Data File : \\Poweredge\\E drive\\TC\\dennis\\LP019-20080503-120610.raw
 Result File : \\Poweredge\\E drive\\TC\\dennis\\LP019-20080503-111807.rst
 Inst Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E drive\\TC\\dennis\\LP019-20080503-111807.rst
 Proc Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH
 Calib Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH
 Sequence File : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	14.158	11895076.20	415761.95	76.77	76.77	BB	28.6103
2	20.866	3598446.80	96817.90	23.23	23.23	BB	37.1672
		15493523.00	512579.85	100.00	100.00		

PROTON CDC13 D:\\ Lukas 1

C13CPD CDCl3 D:\\ Lukas 1

Software Version : 6.1.2.0.1:D19 Date : 8/13/08 1:38:32 AM
 Operator : manager Sample Name : B96 PhQ
 Sample Number : 10%IPA tst Study :
 AutoSampler : SER200 Rack/Vial : 0/3
 Instrument Name : LC Channel : B
 Instrument Serial # : None A/D mV Range : 1000
 Delay Time : 0.00 min End Time : 29.99 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul Area Reject : 0.000000
 Sample Amount : 1.0000 Dilution Factor : 1.00
 Data Acquisition Time : 7/10/08 12:27:31 PM Cycle : 233

Raw Data File : \\Poweredge\\E drive\\TC\\dennis\\LP049-20080710-122748.raw
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 drive\\TC\\dennis\\LP049-20080710-113250.rst
 Proc Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E
 drive\\TC\\dennis\\LP049-20080710-113250.rst
 Calib Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E
 drive\\TC\\dennis\\LP049-20080710-113250.rst
 Sequence File : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	4.567	956799.18	67668.78	3.25	3.25	MM	14.1394
2	15.340	22332495.71	724933.06	75.90	75.90	MM	30.8063
3	16.687	6135571.41	181761.33	20.85	20.85	MM	33.7562
		29424866.30	974363.18	100.00	100.00		

B41-2: Intra CC BINAP w KCO3
 PROTON CDC13 D:\\ Lukas 1

Software Version : 6.1.2.0.1:D19 Date : 4/28/08 12:33:02 PM
 Operator : manager Sample Name : B87-THF BnQ
 Sample Number : SER200 Study : chirals
 AutoSampler : LC Rack/Vial : 0/1
 Instrument Name : None Channel : B
 Instrument Serial # : 0.00 min A/D mV Range : 1000
 Delay Time : 2.5000 pts/s End Time : 31.99 min
 Sampling Rate : 1.000000 ul Area Reject : 0.000000
 Volume Injected : 1.0000 Dilution Factor : 1.00
 Sample Amount : 4/28/08 1:18:43 PM Cycle : 88
 Data Acquisition Time :

Raw Data File : \\Poweredge\\E drive\\TC\\dennis\\LP018-20080428-131902.raw
 Result File : \\Poweredge\\E drive\\TC\\dennis\\LP018-20080428-123302.rst
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 drive\\TC\\dennis\\LP018-20080428-123302.rst
 Proc Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH
 Calib Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH
 Sequence File : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	5.602	55244.00	5785.35	0.09	0.09	BB	9.5821
2	7.527	60407.20	4708.27	0.11	0.11	BB	14.7415
3	18.064	13583358.40	331823.12	21.23	21.23	BB	40.9355
4	23.798	50288323.60	805858.08	78.58	78.58	BB	62.4034
		63996333.20	1.15e+06	100.00	100.00

Sample Name : B87-THF BnQ
 File Name : \\Poweredge\\E drive\\TC\\dennis\\LP018-20080428-131902.raw
 Date : 4/28/08 12:33:02 PM
 Method : Cpak ADH.mn
 Start Time : 0.00 min
 End Time : 31.99 min
 Time of Injection : 4/28/08 1:18:43 PM
 Low Point : 31.75 mV
 High Point : 818.52 mV
 Scale Factor : 1.0
 PPM Offset : 31.25 mV
 PPM Scale : 847.8 mV

Page 1 of 1

PROTON CDC13 D:\\ Lukas 1

CI3CPD CDC13 D:\\ Lukas 1

Chromatogram

Sample Name: C8 OMBQQ Cs
 File Name: I:\Poweredge\drive\TC\dennis\LP043-20080628-071740.raw
 Method: 8/1/08 12:40:02 PM
 Start Time: 0:00 min
 End Time: 44:59 min
 Port Choke: -14.88 mV
 High Point: 277.42 mV
 Low Point: -14.88 mV
 Post Scale: 282.1 mV

Software Version : 6.1.2.0.1:019
 Operator : manager
 Sample Number :
 AutoSampler : SER200
 Instrument Name : LC
 Instrument Serial # : None
 Delay Time : 0.00 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul
 Sample Amount : 1.0000
 Data Acquisition Time : 8/28/08 7:17:37 AM

Date : 8/1/08 12:40:02 PM
 Sample Name : C8 OMBQQ Cs
 Study :
 Rack/Vial : 0/6
 Channel : 8
 A/D mV Range : 1000
 End Time : 44:59 min
 Area Reject : 0.000000
 Dilution Factor : 1.00
 Cycle : 169

Raw Data File : I:\Poweredge\drive\TC\dennis\LP043-20080628-071740.raw
 Result File : I:\Poweredge\drive\TC\dennis\LP043-20080628-063932.rst
 Inst Method : I:\Poweredge\drive\TC\dennis\Cpak ADH from I:\Poweredge\drive\TC\dennis\LP043-20080628-063932.rst
 Proc Method : I:\Poweredge\drive\TC\dennis\Cpak ADH from I:\Poweredge\drive\TC\dennis\LP043-20080628-063932.rst
 Calib Method : I:\Poweredge\drive\TC\dennis\Cpak ADH from I:\Poweredge\drive\TC\dennis\LP043-20080628-063932.rst
 Sequence File : I:\Poweredge\drive\TC\dennis\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL Area/Height [s]
1	4.507	518615.60	25181.78	1.44	1.44	BB 20.6112
2	6.646	77203.00	1321.17	0.21	0.21	BB 58.4358
3	8.886	57626.20	1231.07	0.16	0.16	BB 48.8091
4	30.718	438960.00	54074.89	12.22	12.22	BB 81.1828
5	35.709	3089922.40	269186.78	85.96	85.96	BB 114.6764
		35813316.80	350875.70	100.00	100.00	

PROTON CDC13 D:\ Lukas 1

Chromatogram

Sample Name : C9 DMAQ Cs
 File Name : \\poweredge\I drive\TC\dennis\LP046-20080702-115855.raw
 Date : 7/2/08 11:19:41 AM
 Method : C:\ADH.mh
 Start Time : 0:00 min
 Scale Factor : 1.0
 Page 1 of 1
 Sample # : 802PA 1st
 Time of Injection : 7/2/08 11:50:41 AM
 Low Point : -47.41 mV
 High Point : 948.21 mV
 End Time : 44.99 min
 Plot Offset : -47.41 mV
 Plot Scale : 985.6 mV

Software Version : 6.1.2.0.1:D19
 Operator : manager
 Sample Number : 8%IPA 1st
 AutoSampler : SER200
 Instrument Name : LC
 Instrument Serial # : None
 Delay Time : 0.00 min
 Sampling Rate : 2.5000 pts/s
 Volume Injected : 1.000000 ul
 Sample Amount : 1.0000
 Data Acquisition Time : 7/2/08 11:58:41 AM
 Date : 7/2/08 11:19:41 AM
 Sample Name : C9 DMAQ Cs
 Study :
 Rack/Vial : 0/1
 Channel : B
 A/D mV Range : 1000
 End Time : 44.99 min
 Area Reject : 0.000000
 Dilution Factor : 1.00
 Cycle : 195

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 Calib Method : \\poweredge\I drive\TC\dennis\Cpak ADH
 Sequence File : \\poweredge\I drive\TC\dennis\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL Area/Height [s]
1	4.623	1096045.40	79292.87	1.81	1.81	BB 13.8227
2	7.857	30114.40	2414.76	0.05	0.05	BB 12.4710
3	13.204	36226930.40	942618.40	59.92	59.92	BB 38.4322
4	16.983	22615845.60	451098.36	37.41	37.41	BB 50.1351
5	27.216	486170.00	637.59	0.80	0.80	BB 762.5121
		60455105.80	1.48e+06	100.00	100.00	

one spot on TLC

Chromatogram

Page 1 of 1
Sample # 175094 uc
Injection Volume 10 µl
Date 7/16/06 11:24:35 AM
Method : \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-122027.rst
Time of Injection: 7/16/06 12:45:19 PM
End Time : 89.99 min
Start Time : 0.00 min
Low Point : -3.59 mV
High Point : 88.13 mV
Pulse Count: 117 mV

Software Version : 6.1.2.0.1.D19
Operator : manager
Sample Number : 175094 uc
AutoSampler : SER200
Instrument Name : LC
Instrument Serial # : None
Delay Time : 0.00 min
Sampling Rate : 2.5000 pts/s
Volume Injected : 1.000000 µl
Sample Amount : 1.0000
Data Acquisition Time : 7/16/06 12:45:19 PM
Date : 7/16/06 11:24:35 AM
Sample Name : C7 8-10 repur
Study :
Rack/Vial : 0/4
Channel : 8
A/D mV Range : 1000
End Time : 89.99 min
Area Reject : 0.000000
Dilution Factor : 1.00
Cycle : 240

Raw Data File : \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-124533.raw
Result File : \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-122027.rst
Inst Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-122027.rst
Proc Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-122027.rst
Calib Method : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH from \\Poweredge\\E drive\\TC\\dennis\\LP049-20080714-122027.rst
Sequence File : \\Poweredge\\E drive\\TC\\dennis\\Cpak ADH.seq

DEFAULT REPORT

Peak #	Time [min]	Area [µV s]	Height [µV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
1	4.501	1231752.20	62465.31	12.94	12.94	BB	19.7190
2	6.558	55136.00	2421.68	0.98	0.98	BB	22.7676
3	8.007	59469.80	1561.15	0.62	0.62	BB	38.0835
4	11.113	221406.40	711.24	2.33	2.33	BB	311.2982
5	29.140	806972.06	8650.65	8.48	8.48	MM	93.2845
6	35.953	3885809.01	30842.92	40.81	40.81	MM	97.5282
7	40.247	3260587.28	30140.84	34.25	34.25	MM	106.1784
		9521142.56	145793.89	100.00	100.00		

chxpyall R,R: note: ON rxn dried up
 PROTON CDCl3 D:\ Lukas 1

(54)

chxpyall R,R: note: ON rxn dried up
 C13CPD CDCl3 D:\ Lukas 1

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PROTON CDCl3 D:\ Lukaa 1

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