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An Efficient Synthesis of Bridged Heterocycles from an Ir(I) Bis-Amination/ Ring-Closing Metathesis Sequence

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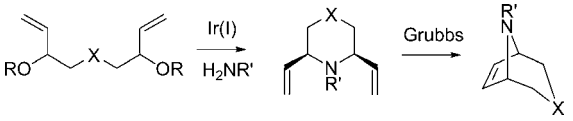
ABSTRACT



The amination of bis-allylic imidates using an Iridium(I) catalyst leads to the efficient formation of 2,6-divinyl heterocycles. Careful screening of amines, solvents, and conditions has led to the discovery of a system that favors formation of the desired *cis* products with synthetically useful levels of diastereoselectivity, and these results are further explained by computer based transition state energy calculations. Exposure of the heterocycles to ring-closing metathesis catalysts leads to the desired bridged heterocyclic systems.

Bridged heterocycles are popular building blocks for medicinal chemists, and they have been used as key components for a variety of pharmaceutical agents.[1] Drug targets containing bridged heterocycles often have similar physiochemical properties as their unbridged counterparts, while the more rigid bridged structure can impart additional potency and target selectivity.[2] Despite continued interest in these building blocks, there remain a few concise synthetic routes to form bridged heterocycles. The routes reported generally suffer from low product yields as a consequence of lengthy syntheses.[3] Herein we report a concise synthesis of a number of nitrogen containing bridged heterocyclic compounds through an iridum catalyzed bis-allylic amination/Grubbs ring-closing metathesis (RCM) sequence. We also provide a mechanistic hypothesis to explain the stereochemical course of these reactions.

The metal catalyzed amination of allylic acetates was originally reported using either basic conditions or a palladium catalyst system.[4] More recently iridium[5] and rhodium catalyzed aminations have emerged as reliable conditions for the selective synthesis of allylic amines from allylic alcohols, esters, carbonates, or imidates.[6] While there are a few examples in the literature of bis-allylic aminations for the formation of heterocycles, the diastereoselectivity is typically poor or strongly favors the *trans* isomer, which is not suitable to RCM.[7] To form the desired bridged system using an RCM strategy we would need to first find bis-allylic amination conditions that favored the formation of *cis* divinyl azine precursors

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(**4**–**6**).[8] These heterocycles would be derived from acyclic bis-allylic alcohols, protected to form a more reactive allylic system.

Scheme 1. Formation of Bis-allylic Alcohols **2** from Cyclic Diols[a]

1a, X = O
1b, X = CH_2
1c, X = N-Boc

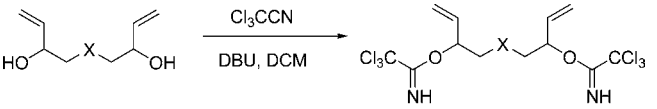
2a, X = O, 79%
2b, X = CH_2, 85%
2c, X = N-Boc, 62%

[a] Yields refer to purified material after isolation by column chromatography over silica gel.

The synthetic sequence began with cyclic diols **1**, which were commercially available in the cases of **1a** (X = O) and **1b** (X = CH_2), or could be formed in a single step by a dihydroxylation of commercially available N-Boc 2,5-dihydropyrrole in the case of **1c** (X = N-Boc).[9] Oxidative cleavage of the diol with di(acetoxy)iodobenzene in DCM, followed by addition of vinylmagnesium bromide to the crude dialdehyde at low temperature, cleanly afforded the desired bis-allylic alcohols **2** (Scheme 1).[10] Attempts to purify the dialdehyde were unsuccessful due to issues with stability and volatility, favoring the one-pot procedure.

While there are examples of allylic amination reactions on allylic alcohols, this reactivity typically favors mono-amination and does not provide the desired heterocycles in our system.[6] The desired product could be formed using a bis-allylic acetate or bis-allylic carbonate, but the reactivity was poor and the reactions only went to completion at high temperatures, resulting in low levels of diastereoselectivity. Nguyen reported that an allylic imidate is a highly reactive leaving group for allylic amination, allowing the addition of secondary amines which were not reactive with acetates or carbonates.[6i] Diols **2** were converted to the desired bis-imidates **3** in good yields using trichloroacetonitrile and DBU (Scheme 2).

Scheme 2. Formation of Bis-imidates **3** from Diols **2**[a]



2a, X = O
2b, X = CH_2
2c, X = N-Boc

3a, X = O, 72%
3b, X = CH_2, 67%
3c, X = N-Boc, 60%

[a] Yields refer to purified material after isolation by column chromatography over silica gel.

With the desired bis-imidates in hand, a variety of reaction conditions were screened to determine which combination of catalyst, amine, and solvent would lead to selective formation of the desired 2,6-*cis* heterocycles. When bis-imidate **3a** was exposed to a primary benzylamine derivative in the presence of an iridium(I) catalyst the major product was the desired divinyl morpholine **4**. Palladium(0) gave the product in lower yields. Amides, carbamates, and sulphonamides proved to be poor reaction partners, giving little to no desired products under a variety of conditions. Benzylamine gave the product in acceptable yield, but the diastereoselectivity was poor and slightly favored the undesired *trans* diastereomer (Table 1). Reactions with tritylamine as the nitrogen source gave high yields but poor selectivity under a variety of conditions. Cumylamine proved to be the best nitrogen source for the allylic amination reactions, providing the desired morpholine product in high yields and favoring the desired *cis* isomer, which was assigned based on ^{1}H NMR analysis. After screening a number of solvents it was found that dichloroethane and toluene both gave moderate diastereoselectivity, favoring the desired 2,6-*cis* isomer of morpholine **4**. More polar solvents typically gave good yields but poor diastereoselectivity.[11]

Further reaction optimization found that the best catalyst for the bis-allylic amination reaction was the commercially available $[Ir(cod)Cl]_2$, and the optimum conditions were found when the reaction was run in dichloroethane starting at 0 °C and allowed to warm slowly to room temperature over 18 h (2 h of warming followed by 16 h at ambient temperature; see Table 2). Reactions in toluene also gave good levels of selectivity but typically gave slightly lower yields. Reactions at lower temperature gave lower yields due to incomplete conversion. Careful workup was necessary to remove the catalyst, since it is highly soluble in a variety of organic solvents. Prolonged exposure

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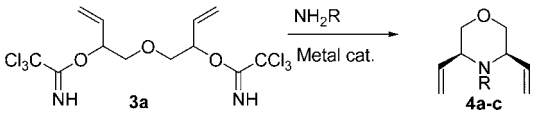
(8) For some reviews of ring closing metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (d) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. For examples of RCM to form bridged systems, see: (e) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469–1471. (f) Kuznetsov, N. Y.; Khrustalev, V. N.; Godovikov, I. A.; Bobnov, Y. N. *Eur. J. Org. Chem.* **2006**, 113–120. (g) Cheng, G.-L.; Wang, X.-Y.; Zhu, R.; Shao, C.-W.; Xu, J.-M.; Hu, Y.-F. *J. Org. Chem.* **2011**, *76*, 2694–2700.

(9) N-Boc dihydropyrrole was dihydroxylated using OsO_4/NMO conditions; see Supporting Information for details.

(10) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552–1555.

(11) Reactions in propionitrile, DMSO, diglyme, and diethyl ether also gave moderate yields and low levels of diastereoselectivity. Reactions did not proceed in heptane, presumably due to poor solubility

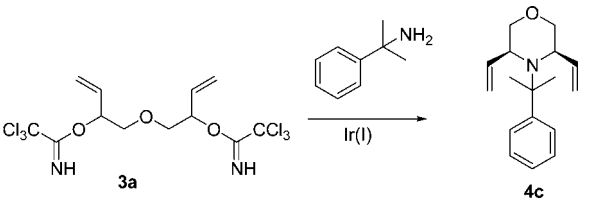
Table 1. Diastereoselective Bis-allylic Amination To Form **4**[a]



amine	catalyst	solvent	temp	yield[b]	dr[c]	product
$BnNH_2$	$[Ir(cod)Cl]_2$	MeCN	60 °C	42	1:1.3	**4a**
$BnNH_2$	$Pd(PPh_3)_4$	MeCN	rt	32	1:1	**4a**
$BnNH_2$	$[Ir(cod)Cl]_2$	DCE	rt	trace	N/A	**4a**
$tritylNH_2$	$[Ir(cod)Cl]_2$	MeCN	60 °C	64	1.1:1	**4b**
$tritylNH_2$	$[Ir(cod)Cl]_2$	MeCN	rt	92	1.1:1	**4b**
$tritylNH_2$	$[Ir(cod)Cl]_2$	THF	rt	76	1.1:1	**4b**
$tritylNH_2$	$[Ir(cod)Cl]_2$	DCE	rt	62	1.1:1	**4b**
$cumylNH_2$	$[Ir(cod)Cl]_2$	MeCN	60 °C	52	1.4:1	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	MeCN	rt	61	1.3:1	**4c**
$cumylNH_2$	$[Ir(cod)OMe]_2$	MeCN	rt	65	1.5:1	**4c**
$cumylNH_2$	$Pd(PPh_3)_4$	MeCN	rt	trace	N/A	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	THF	rt	58	2.0:1	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	dioxane	rt	54	2.3:1	**4c**
$cumylNH_2$	**$[Ir(cod)Cl]_2$**	**DCE**	**rt**	**53**	**3.5:1**	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	DCM	rt	57	2.2:1	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	$CHCl_3$	rt	55	1.3:1	**4c**
$cumylNH_2$	**$[Ir(cod)Cl]_2$**	**toluene**	**rt**	**66**	**3.7:1**	**4c**
$cumylNH_2$	$[Ir(cod)Cl]_2$	DMF	rt	75	1.2:1	**4c**

[a] All reactions run at 0.2 M in the indicated solvent with 5 mol % catalyst. [b] Yields refer to purified material after isolation by column chromatography over silica gel. All yields refer to a mixture of diastereomers. [c] Diastereomeric ratio determined by ^1H NMR analysis of the crude reaction mixture.

Table 2. Optimization of Bis-allylic Amination Conditions[a]



solvent	catalyst	temp	time (h)	yield[b]	dr[c]
DCE	$[Ir(cod)Cl]_2$	rt	18	53	3.5:1
DCE	$[Ir(cod)Cl]_2$	0 °C	3	68	5.1:1
DCE	$[Ir(cod)OMe]_2$	0 °C	3	73	4.4:1
DCE	$[Ir(cod)Cl]_2$	0 °C to rt	18	79	5.1:1
DCE	$[Ir(cod)OMe]_2$	0 °C to rt	18	74	4.7:1
DCE	$[Ir(cod)Cl]_2$	−15 °C to rt	18	70	4.9:1
toluene	$[Ir(cod)Cl]_2$	−20 °C	18	39	4.2:1
toluene	$[Ir(cod)Cl]_2$	rt	18	66	3.7:1
toluene	$[Ir(cod)OMe]_2$	rt	18	66	4.2:1
toluene	$[Ir(cod)Cl]_2$	0 °C	3	45	4.3:1
toluene	$[Ir(cod)OMe]_2$	0 °C	3	47	2.4:1
toluene	$[Ir(cod)Cl]_2$	0 °C to rt	18	59	5.1:1

[a] All reactions run at 0.2 M in the indicated solvent with 5 mol % catalyst. [b] Yields refer to purified material after isolation by column chromatography over silica gel. All yields refer to a mixture of diastereomers. [c] Diastereomeric ratio determined by ^1H NMR analysis of the crude reaction mixture.

can lead to reinsertion into the allylic system of the product and a complete loss of diastereoselectivity. When the purified product was re-exposed to the catalyst system in a polar organic solvent, a loss of diastereoselectivity was observed over time. This effect was not observed in dichloroethane. Direct purification of the crude reaction mixture by silica gel chromatography was found to be the best way to remove the catalyst. The two diastereomers could not be separated using standard chromatographic techniques, so all yields refer to the mixture of diastereomers. These diastereomeric mixtures were taken on to the subsequent RCM step without further purification.

In order to investigate the impact of temperature on the diastereoselectivity observed in dichloroethane, computational models for the *cis* and *trans* transition states and products were obtained at a high level of theory. As shown in Figure 1 the computations modeled the transition states leading to the *cis* and *trans* products for the second allylic amination step. The energy difference at the B3LYP/LACV3P**+//B3LYP/LACV3P* level between the two TS models is 0.73 kcal/mol favoring the *cis* isomer consistent with a kinetically controlled formation. Addition of zero-point vibrational energies and thermal contributions at 0 °C to enthalpy provided a *cis* TS more enthalpically favorable by 0.74 kcal/mol. Addition of entropic contributions led to a reduced free-energy difference in the gas phase of 0.33 kcal/mol. Incorporation of dichloroethane solvent effects provided a final value of 0.98 kcal/mol or a diastereomeric ratio of 6.1:1, very close to the most selective conditions in Table 2. In the case of the less selective conditions at room temperature, it is plausible that the diastereoselectivity is thermodynamically controlled. Therefore, models for the *cis* and *trans* products were obtained in the gas phase. The energy difference at the B3LYP/6-311G**+ level between the two products was 0.25 kcal/mol favoring the *trans* isomer. Addition of zero-point vibrational energies and thermal contributions at 25 °C to enthalpy and entropy led to a free-energy difference of 0.48 kcal/mol now favoring the *cis* isomer. Incorporation of DCE solvent effects brought the free-energy difference to a final value of 0.71 kcal/mol, or a 3.3:1 diastereomeric ratio, in excellent agreement with the experimental value in Table 2.

Bis-imidates **3b** and **3c** also underwent the desired iridium(I) catalyzed cyclization with cumylamine to form piperidine **5** and piperazine **6** respectively (Scheme 3). Piperidine **5** was formed in 67% yield as a 3.5:1 mixture of diastereomers when the reaction was run at 0 °C for 3 h. Allowing this reaction to warm to room temperature resulted in a loss of diastereoselectivity. The bis-allylic amination to form piperazine **6** gave the desired product in 84% yield as a 12:1 mixture of diastereomers. Both reactions favored the desired 2,6-*cis* isomer of the heterocycle.

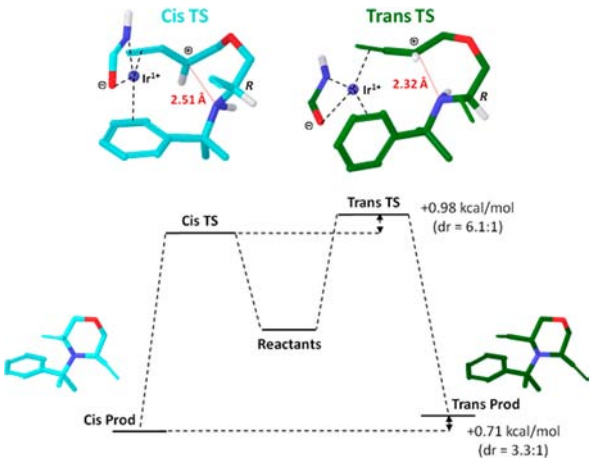
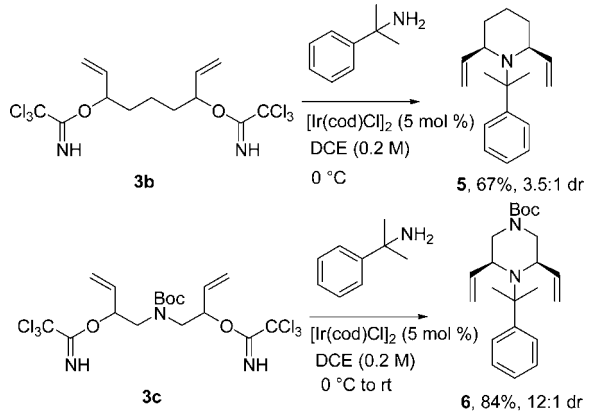


Figure 1. Model for the *cis* and *trans* transition states and products. See Supporting Information for a full size model and more details on the calculations and assumptions built into this transition state model.

Scheme 3. Formation of Piperidine **5** and Piperizine **6**[a]

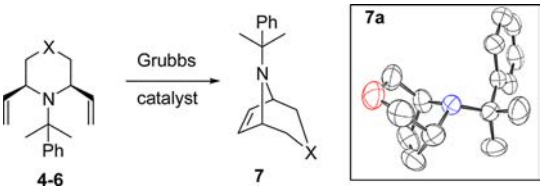


[a] Yield refers to purified material after isolation by column chromatography over silica gel. All yields refer to a mixture of diastereomers. Diastereomeric ratio determined by ^{1}H NMR analysis of crude reaction mixtures.

With the divinyl azine heterocycles in hand, conditions were screened for the Grubbs ring-closing metathesis to form the desired bridged heterocyclic products. Treatment of diene **4** (as a mixture of diastereomers) with Grubbs' second generation catalyst in toluene at 120 °C gave clean conversion of the *cis* isomer to desired bridged heterocycle **7a** (Table 3). The structure of **7a** was confirmed by X-ray crystallography. This reaction also worked for the piperidine **5** leading to product **7b**, albeit in lower yield, presumably due to the greater basicity of the piperidine nitrogen. Additions of acid led to decomposition of the starting materials, while increasing the temperature by using xylenes as a solvent gave a modest increase in yield. Piperazine **6** gave clean conversion to bridged ring system **7c**. The cumyl group of product **7a** could be easily removed using TFA, to afford the secondary amine salt.[12]

(12) For structure of the RCM catalysts and details on the selective removal of the cumyl protecting group after cyclization, see Supporting Information.

Table 3. Grubbs Metathesis To Form Bridged Heterocycles[a]



X	catalyst	solvent	temp	yield[b]	product
O	Hoveyda-Grubbs 2	DCM	rt	3	**7a**
O	Grubbs 2	DCM	rt	17	**7a**
O	Grubbs 2	DCE	90 °C	25	**7a**
O	Grubbs 2	toluene	120 °C	79	**7a**
CH_2	Grubbs 2[c]	toluene	120 °C	29	**7b**
CH_2	Grubbs 2[c]	xylenes	150 °C	34	**7b**
NBoc	Grubbs 2	toluene	120 °C	82	**7c**

[a] All reactions run with 5 mol % catalyst in the specified solvent (0.08 M). [b] Yields refer to purified material after isolation by column chromatography over silica gel. [c] Reactions run with 10 mol % catalyst.

In conclusion, a straightforward, efficient sequence was developed to prepare bridged heterocycles. A one-pot oxidative cleavage/Grignard addition gave direct access to the key bis-allylic alcohols. Iridium(I) catalyzed bis-allylic amination gave the desired heterocycles, with the *cis* isomer predominating. Computations suggest that under kinetically controlled conditions coordination to the iridium catalyst gives rise to a more stable *cis* transition state. Grubbs' ring closing metathesis finished the sequence, forming the desired bridged heterocycles in good yield. The products will be used as intermediates for potential pharmaceutical development.

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Supporting Information Available. Preparation and characterization of all compounds is included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.