

2.3. Synthesis of protected hydroxymethyl bicycle **2.04** insertion substrates

With the optimized conditions for the allylic methyl group insertion identified by Dr. Valette and Professor Huw M. L. Davies, we decided to approach the synthesis of the protected hydroxymethyl series **2.04**. Professor Erik J. Sorensen, Aaron Bedell, and I imagined that in order to observe a productive allylic methyl group insertion, we needed to thoroughly deactivate the vicinal hydroxymethyl groups, which meant to us that we needed to protect them with electron-withdrawing substituents. We identified a route to accessing the desired protected hydroxymethyl 5,5-bicyclic series **2.04** that allowed for late-stage incorporation of protecting groups, which allowed us the opportunity to synthesize a bulk amount of late-stage intermediate that we could then diversify the protecting group and access our desired insertion substrates.

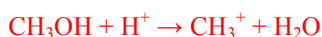
Initially, we would utilize acetate and pivalate protecting groups to test the C–H/Cope strategy (Scheme 2.13). In order to access this material, we started by treating known tetraester **2.40**¹⁴ with sodium hydride and 1,1-bis(chloromethyl)ethylene **2.41** in warm *N,N*-dimethylformamide; this reaction accomplished a double alkylation-cyclization in 95% yield. Exhaustive reduction of the resulting cyclic tetraester with LiAlH₄ was accomplished in 20-25% yield to give tetraol **2.42**.¹⁵ Attempts at working up the reaction mixture proved to be extremely difficult to separate the product from the water and alumina byproducts. To make matters more challenging, the product tetraol **2.42** is quite soluble in water and treatment with acid leads to product decomposition, which limited the workup conditions to basic conditions to access the product. Next,

Seeded Content – **Wikipedia *Methyl Group***
https://en.wikipedia.org/wiki/Methyl_group

A methyl group is an [alkyl](#) derived from [methane](#), containing one [carbon](#) atom [bonded](#) to three [hydrogen](#) atoms — CH₃. In [formulas](#), the group is often [abbreviated](#) Me. Such [hydrocarbon](#) groups occur in many [organic compounds](#). It is a very stable group in most molecules. While the methyl group is usually part of a larger [molecule](#), it can be found on its own in any of three forms: [anion](#), [cation](#) or [radical](#). The anion has eight valence electrons, the radical seven and the cation six. All three forms are highly reactive and rarely observed.^[1]

Methyl cation

The methylium cation (CH₃⁺) exists in the [gas phase](#), but is otherwise not encountered. Some compounds are considered to be sources of the CH₃⁺ cation, and this simplification is used pervasively in organic chemistry. For example, [protonation](#) of methanol gives a strongly electrophilic methylating reagent:



Similarly, [methyl iodide](#) and methyl [triflate](#) are viewed as the equivalent of the methyl cation because they readily undergo S_N2 reactions by weak [nucleophiles](#).

Methyl anion

The methanide anion (CH₃[−]) exists only in rarefied gas phase or under exotic conditions. It can be produced by electrical discharge in [ketene](#) at low pressure (less than one [torr](#)) and its [enthalpy of reaction](#) is determined to be about 252.2±3.3 [kJ/mol](#).^[2]

In discussions mechanisms of organic reactions, [methyl lithium](#) and related [Grignard reagents](#) are often considered to be salts of "CH₃[−]"; and though the model may be useful for description and analysis, it is only a useful fiction. Such reagents are generally prepared from the methyl halides:



where M is an alkali metal.

Methyl radical

Main article: [Methyl radical](#)

The methyl [radical](#) has the formula CH₃. It exists in dilute gases, but in more concentrated form it readily [dimerizes](#) to [ethane](#). It can be produced by [thermal decomposition](#) of only certain compounds, especially those with an -N=N- linkage.

Reactivity

The reactivity of a methyl group depends on the adjacent [substituents](#). Methyl groups can be quite unreactive. For example, in organic compounds, the methyl group resists attack by even the strongest [acids](#).

Oxidation

The [oxidation](#) of a methyl group occurs widely in nature and industry. The oxidation products derived from methyl are CH₂OH, CHO, and CO₂H. For example, [permanganate](#) often converts a methyl group to a carboxyl (-COOH) group, e.g. the conversion of [toluene](#) to [benzoic acid](#). Ultimately oxidation of methyl groups gives [protons](#) and [carbon dioxide](#), as seen in combustion.

Methylation

Main article: [Methylation](#)

Demethylation (the transfer of the methyl group to another compound) is a common process, and [reagents](#) that undergo this reaction are called methylating agents. Common methylating agents are [dimethyl sulfate](#), [methyl iodide](#), and [methyl triflate](#). [Methanogenesis](#), the source of natural gas, arises via a demethylation reaction.^[3]

2.5. Initial C–H/Cope attempts using THF-containing bicycle series

With both THF-containing 5,5-bicycle series in hand, we were able to begin our studies on performing a C–H insertion and, ultimately, the C–H/Cope reaction on the allylic methyl group of the substrates. We initially decided that, since we had identified successful conditions to perform primary allylic C–H insertion on the all-carbon analog (See Section 2.2), that first attempting to see if C–H insertion was possible before taking the next step to trying the C–H/Cope reaction was the best course of action.

Our initial C–H insertion attempt began with dimethyl THF-containing 5,5-bicycle **2.49** with methyl phenyldiazoacetate **2.14a** in the presence of $\text{Rh}_2(\text{S-DOSP})_4$ (Scheme 2.15). The first attempt to selectively insert into the primary allylic methyl C–H bond of dimethyl THF-containing 5,5-bicycle **2.49** did not yield any products resembling desired insertion product **2.50**. Instead, what was isolated was a product of insertion into the α -methylene insertion of the THF ring in a 49% yield and >20:1 d.r., which has been observed previously by the Davies group in less complex settings.^{6,7} Moreover, 2D NMR suggested to Dr. Valette that the diastereomer isolated was the product of C–H insertion on the concave face of the substrate and on the same side of the alkene within the cyclopentene ring, which is the same stereochemistry as that of the indoxamycins with an alkene functional handle to permit an eventual annulation of the six-membered ring.

2.6. Redesigned retrosynthetic analysis of indoxamycin F and the rest of the family members

With the extensive amount of evidence that the desired C–H/Cope transformation that we had initially identified as the first C–H functionalization *en route* to the synthesis of indoxamycin F and the rest of the family members, we decided that instead of fighting the α -methylene THF insertion that we've shown in this system, we would utilize this transformation in a new approach to the synthesis. We thought that we could retain the original idea of a late-stage α -methylene THF ring insertion of tricycle **2.54**, forming the bond highlighted in green. In order to access tricycle **2.54**, we envisioned that we could forge the six-membered ring of the tricycle through a palladium-catalyzed *ortho*-C–H olefination of Davies insertion product **2.55** to furnish the bond highlighted in blue.¹⁷ In order to maximize the likelihood that this reaction is successful, we thought that we needed to activate the pendant olefin by activating it through making it part of an α,β -unsaturated ester. This allowed us to be able to take advantage of the inherent reactivity that we had initially discovered in the THF-containing 5,5-bicycle series **2.04**. We envisioned that we could utilize the inherent reactivity we had discovered in the THF-containing 5,5-bicycles and expand it further to perform the C–H insertion on the α -methylene of the THF ring of enoate **2.56** to form the bond highlighted in red.^{6a-c} We thought this provided the ideal approach with the minimal amount of change necessary to try the alternative route.

2.7. Synthesis of enoate **2.56**

In order for us to be able to assess whether we can utilize enoate **2.56** for our first of three C–H functionalizations, we needed to develop a synthetic route that would allow us to access material quickly and efficiently, as previous routes for earlier compounds **2.44**, **2.46**, and **2.49** all had their faults for one reason or another. For compounds **2.44** and **2.46**, the reduction of the alkylated tetraester proved to be a significant bottleneck to material throughput. Working with compound **2.49** proved to be difficult as well, as the material was highly volatile, making isolation extremely difficult. With this new route, we hoped to be able to easily access a compound that would be significantly easier to work with.

We were able to devise a route to accessing enoate **2.56** through a simple procedure involving three steps from previously described enone **2.47**. First, 1,4-addition of a methyl group catalyzed by copper (I) iodide and lithium chloride in THF at –40 °C with trapping of the resulting enolate with trimethylsilyl chloride (TMSCl) forms TMS-silyl enol ether **2.57**.¹⁸ Next, the crude product was subjected to conversion of the silyl enol ether to the vinyl triflate facilitated by potassium *tert*-butoxide and Comins' reagent in THF at –78 °C to give enol triflate **2.58**.¹⁹ Subjecting enol triflate **2.58** to palladium-catalyzed carbonylation conditions furnished the methyl ester in enoate **2.56** in a 62% overall yield over the three steps.²⁰

2.8. Probing the α -methylene THF insertion of enoate **2.56**

With enoate **2.56** in hand and a practical route to easily access synthetically useful quantities of it, we were able to do initial studies to assess if the racemic enoate **2.56** was a suitable substrate for α -methylene THF insertion. Preliminary studies with simple, achiral dirhodium carboxylates (Table 2.5, Entries 1 and 2) demonstrated little to no C–H insertion reactivity, resulting only in the decomposition of **2.14a** and recovery of the unreacted bicyclic ester. Previously established conditions known to favor ethereal C–H insertion of donor/acceptor carbenes^{6d,17} suggested $\text{Rh}_2(\text{DOSP})_4$ ²¹ and $\text{Rh}_2(\text{PTAD})_4$ ²² as most likely to effect the desired transformation. Indeed, (\pm)-**2.56**, when treated with two equivalents of donor/acceptor diazo compound **2.14d** in the presence of $\text{Rh}_2(\text{S-DOSP})_4$, produced C–H insertion product **2.55d** in 39% yield and 20:1 dr (49% overall conversion of (\pm)-**2.56**, Table 2.5, Entry 3). Most excitingly, *n*OE studies confirmed that C–H insertion of the rhodium-bound carbene took place adjacent the tetrahydrofuranyl oxygen, exclusively on the concave face of the bicyclo[3.3.0]octane scaffold, and proximal to the α,β -unsaturated ester.

11	(+)- 2.56	Rh ₂ (S-PTAD) ₄	isooctane/TFT (2:1, 55 °C)	72 (97)	>20:1
12	(+)- 2.56	Rh ₂ (S-PTAD) ₄	isooctane/TFT (2:1, 75 °C)	51 (94)	15:1

Table 2.5. Preliminary Davies insertion results with **2.56** and catalyst matching studies.

This result, in light of prior observations by Davies,²³ suggested to us the possibility of a kinetic resolution of (±)-**2.56**. In order to explore this hypothesis, enantioenriched (>97% e.e.) (+)-**2.56** and (-)-**2.56** (see Supporting information) were independently subjected to the previously established reaction conditions in the presence of a single enantiomer of dirhodium catalyst and the conversion to insertion product analyzed by ¹H NMR. The outcomes, summarized in Table 2.5, Entries 4-7, confirmed the existence of a significant matching effect for both Rh₂(DOSP)₄ and Rh₂(PTAD)₄, particularly with the latter catalyst. Using this knowledge, pairing (+)-**2.56** with Rh₂(S-PTAD)₄ provided 95% conversion of (+)-**2.56** to C–H insertion adduct **2.55d** with >20:1 d.r. (Table 2.5, Entry 6).

Emboldened by this validation of the initial design, we sought any possible improvements to the Davies insertion. A systematic variation of the reaction conditions did not yield positive results. The inert, non-polar reaction medium offered by DMB was preferred for reliably high diastereomeric ratios but required the addition of small amounts of TFT to increase the solubilities of both the diazo compound and dirhodium catalyst. The composition of this binary solvent system does, however, limit the temperature range for the Davies insertion and, combined with an unexpected (and currently unresolved) shortage in the

commercial supply of DMB, prompted us to explore an increase in the fraction of TFT used as solvent. However, only decreased conversions and diastereomeric ratios followed (Table 2.5, Entries 8 and 9). Replacing DMB altogether with readily available 2,2,4-trimethylpentane (isooctane) permitted an increase in reaction temperature with a concomitant decrease in conversion (Table 2.5, Entries 10-12). Increased equivalents of donor/acceptor diazo compound were also ineffective in producing higher yields. Ultimately, two equivalents of diazo reagent **2.14** and a binary solution composed of a 2:1 ratio of DMB to TFT were chosen as the optimal trade-off between DMB volume, conversion, and diastereoselectivity.

Having established the viability (and unexpected complexity) of the proposed Davies functionalization, we turned our attention to surveying the scope of donor/acceptor diazo compounds as partners in the reaction. A number of substituted phenylacetic acid derivatives were prepared²⁴ and subjected to the previously described conditions. As from our previous studies, we only worked with the parent methyl phenyldiazoacetate **2.14** and selected 4-substituted derivatives (Table 2.6), as diazo compounds bearing strong electron-donating or most electron-withdrawing groups, substituents at the 2- or 3-positions, or multiple substituents (See section 2.4) did not prove to be competent coupling partners. The parent methyl phenyldiazoacetate **2.14a** and methyl (4-halo)phenyldiazo acetates **2.14b-e** proved to be reliably proficient coupling partners, providing **2.55a-e** in good to excellent isolated yields and diastereomeric ratios (Table 2.6, Entries 1-5). Aryl triflate **2.14f** and

2.11. References

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