

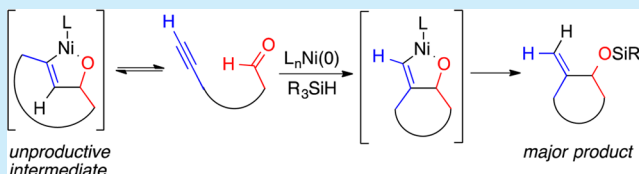
## Exo-Selective Reductive Macrocyclization of Ynals

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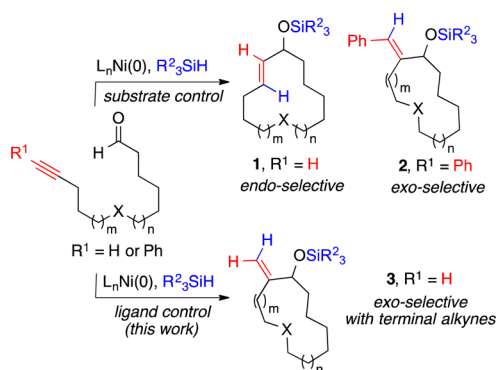
## S Supporting Information

**ABSTRACT:** A general protocol for the highly exo-selective macrocyclization of ynals using a nickel/*N*-heterocyclic carbene catalyst system has been developed. A series of 10- to 21-membered macrocycles bearing an exomethylene substituent was synthesized in good yields with excellent regioselectivity (exo/endo >95:5). Very high levels of long-range diastereocontrol can also be achieved for some classes of macrocycles. Complementary to previously reported endo-selective macrocyclizations, this method provides accesses to exoalkylidene macrocycles from simple ynals in high selectivity.



Macrocycles are common structural motifs in many classes of natural products and bioactive molecules.<sup>1</sup> While methods such as macrolactonization and ring-closing metathesis are commonly employed in their preparation,<sup>2,3</sup> alternative strategies that allow fundamentally different disconnections and precursor functional groups are highly desirable. Nickel-catalyzed reductive coupling methods have proven to be useful in the preparation of macrocycles, since these methods allow the combination of functional groups not commonly employed in macrocycle-forming processes, and both a stereogenic center and a stereodefined alkene are established during assembly of the macrocyclic ring. Reports from our laboratory and the Jamison group have established highly selective reductive macrocyclization methods that were utilized in the synthesis of several natural products.<sup>4</sup> These applications have typically involved control of regiochemistry by the electronic influence of the alkyne. For example, terminal alkynes display a bias toward endocyclization to provide internal 1,2-trans-disubstituted alkenes (Scheme 1, structure 1), whereas aromatic alkynes display a bias toward exocyclization to provide exobenzylidene structural elements (structure 2).

**Scheme 1. Regiocontrol in Nickel-Catalyzed Reductive Macrocyclizations**



In contrast to the ease of assembly of structure types 1 and 2, simple exomethylene substituents are commonly observed in numerous classes of macrolactones,<sup>1b,i</sup> but would require an unfavorable exocyclization from a simple terminal alkyne substrate to afford product 3. A single example of participation of a terminal alkyne in an exo-selective reductive macrocyclization was described by our laboratory while pursuing the total synthesis of 10-deoxymethynolide.<sup>4a</sup> However, the procedure required an *N*-heterocyclic carbene (NHC) ligand that was prepared in a multistep operation and that displays a somewhat limited scope when conducted with minimally functionalized ynal structural classes. Given the potential utility of directly accessing macrocycles of structure type 3 by the reductive exocyclization of simple ynals bearing terminal alkynes, we have conducted studies to provide a more broadly applicable method. As reported herein, a protocol that utilizes a readily available ligand has now been developed that is effective across a range of substrates and that additionally possesses unusual capabilities in long-range diastereocontrol. Mechanistic insights provide a basis for the highly exo-selective outcome of this procedure.

We began the study of exomacrocyclization with ynal 4, by applying reaction conditions that were developed in our recent work with precursors leading to 10-deoxymethynolide.<sup>4a</sup> With ligand DP-IPr and triethylsilane (Et<sub>3</sub>SiH) as the reducing agent (Table 1, entry 1), the desired macrocycle 5 was successfully synthesized with excellent regioselectivity (exo:endo 93:7) albeit in low yield (21%). In the course of conducting recent mechanistic studies of intermolecular aldehyde–alkyne reductive couplings, we observed that high temperatures paired with bulky silanes led to especially high levels of regiocontrol, where the more hindered alkyne terminus undergoes addition to the aldehyde.<sup>5a</sup> In exploring the options with DP-IPr, increasing the reaction temperature did not lead to effective macrocyclizations with substrate 4, and the Ni/DP-IPr catalyzed reaction with

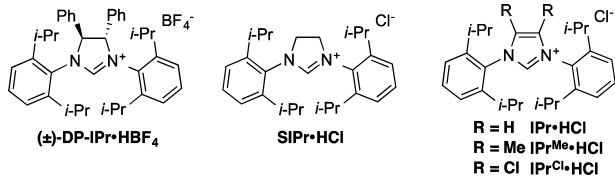
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Table 1. Optimization Study

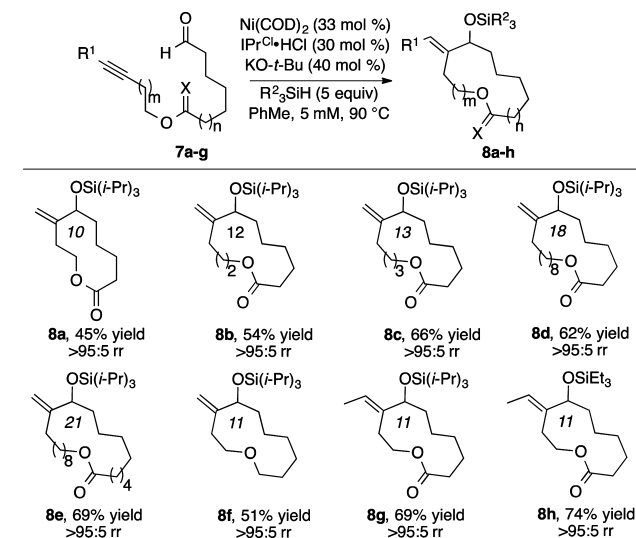
entry	L·HX	temp (°C)	R	C, mM	rr <sup>a</sup> (5:6)	NMR <sup>b</sup> yield, %	isolated yield, %
1	DP-IPr	rt	Et	3	93:7	—	21
2	DP-IPr	90	Et	3	—	trace	—
3	DP-IPr	90	<i>i</i> -Pr	3	—	trace	—
4	SIPr	90	<i>i</i> -Pr	3	>95:5	27	—
5	IPr	90	<i>i</i> -Pr	3	>95:5	18	—
6	IPr <sup>Me</sup>	90	<i>i</i> -Pr	3	>95:5	35	—
7	IPr <sup>Cl</sup>	90	<i>i</i> -Pr	3	>95:5	67	66
8	IPr <sup>Cl</sup>	50	<i>i</i> -Pr	3	>95:5	30	—
9	IPr <sup>Cl</sup>	90	<i>i</i> -Pr	5	>95:5	—	69
10	IPr <sup>Cl</sup>	90	<i>i</i> -Pr	10	>95:5	32	—
11	IPr <sup>Cl</sup>	90	Et	5	65:35	—	51 <sup>c</sup>
12 <sup>d</sup>	IPr <sup>Cl</sup>	90	<i>i</i> -Pr	5	>95:5	17	—
13 <sup>e</sup>	IPr <sup>Cl</sup>	90	<i>i</i> -Pr	5	>95:5	—	63

<sup>a</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture. <sup>b</sup>1,3,5-Trimethoxybenzene was used as the internal standard. Preparative experiments were not conducted with an internal standard due to the complexity of removing the internal standard. <sup>c</sup>Combined yield. <sup>d</sup>Ni(COD)<sub>2</sub> (23 mol %), IPr<sup>Cl</sup>·HCl (20 mol %), KO-*t*-Bu (24 mol %). <sup>e</sup>Ni(COD)<sub>2</sub> (43 mol %), IPr<sup>Cl</sup>·HCl (40 mol %), KO-*t*-Bu (44 mol %).



either Et<sub>3</sub>SiH or (*i*-Pr)<sub>3</sub>SiH as the reducing agent (entries 2 and 3) failed to produce the desired macrocyclization product. Slight improvement of the reaction yield, however, was observed with the SIPr ligand (entry 4). Encouraged by this result, other NHC ligands with 2,6-diisopropylphenyl substituents on nitrogen were examined, and the highest yield of macrocycle **5** was obtained with IPr<sup>Cl</sup> as the ligand (entries 5–7). IPr<sup>Cl</sup> is easily accessible, highly stable, and known to provide highly active catalysts in other catalytic processes.<sup>6,7</sup> With IPr<sup>Cl</sup> as a ligand, the reaction temperature, concentration, and catalyst loading were then investigated. It was found that conducting the reaction at relatively high temperatures (90 °C) was indeed necessary, and lowering the temperature to 50 °C decreased the yield of compound **5** to 30% (entry 8). The concentration of the reaction could be increased to 5 mM (entry 9), but a decrease in yield was observed for the reaction performed at higher concentration (entry 10). The use of bulky (*i*-Pr)<sub>3</sub>SiH was essential for the regioselectivity (exo/endo), and large erosion of the regioselectivity was observed with Et<sub>3</sub>SiH as the reducing agent (entry 11). The optimal catalyst loading for this reaction was 30 mol % of nickel/IPr<sup>Cl</sup>. Lowering the catalyst loading decreased the yield, while increasing the catalyst loading to 40 mol % provided no benefits (entries 12 and 13).

After identifying the optimal reaction conditions (entry 9), the scope of ring size and functional groups tolerated in the exoselective macrocyclization was investigated (Scheme 2). In all cases studied, high selectivity (>95:5) for the formation of exoalkylidene macrocycles was observed. In general, the method

Scheme 2. Scope of Macrocyclizations<sup>a</sup>

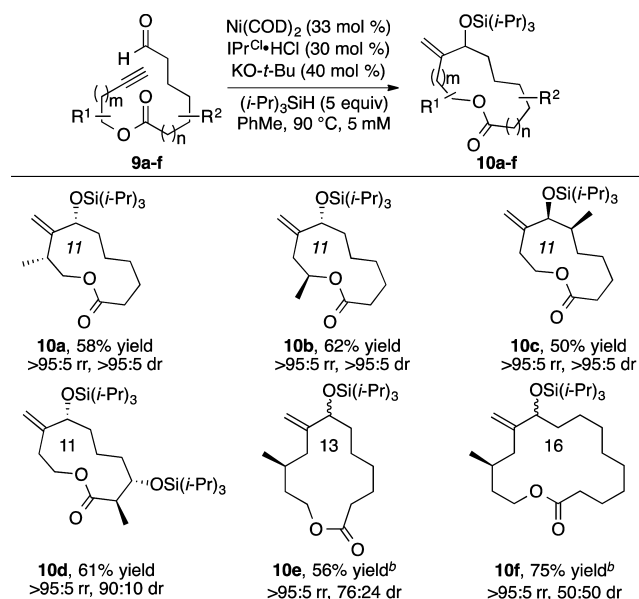
<sup>a</sup>rr is ratio of regioisomers.

worked well in generating molecules having a ring size greater than 11, and 12-, 13-, 18-, and 21-membered macrocycles **8b–8e** were produced in good yields. Under the standard conditions, 10-membered macrocycle **8a** was also successfully synthesized in moderate yield (45%). In addition to esters within the linear precursor, ethers are also tolerated as shown by the synthesis of macrocycle **8f**. Unfortunately, further efforts to include an amide functional group or purely aliphatic chains only resulted in low yields. In these latter cases, dimers and higher oligomers were observed as major products.

In addition to terminal alkynes, the reaction of internal alkynes was also explored. In our previous study on nickel-catalyzed reductive macrocyclizations, a larger ring (21-membered) exoalkylidene macrocycle was prepared using IPr as the ligand and Et<sub>3</sub>SiH as the reducing reagent (exo/endo = 5:1).<sup>4b</sup> Based on the high regioselectivity observed in this study, we envisioned that higher selectivity toward the synthesis of exoalkylidene macrocycles could be achieved with the IPr<sup>Cl</sup> ligand. Indeed, only exocyclization products **8g** and **8h** were obtained from the Ni/IPr<sup>Cl</sup> catalyzed reaction of ynal **7g** (Scheme 2). In contrast to the need for bulky silanes to achieve high levels of regiocontrol with terminal alkynes, excellent regioselectivity was obtained with both Et<sub>3</sub>SiH and (*i*-Pr)<sub>3</sub>SiH using IPr<sup>Cl</sup> as the ligand.

Prior advances from Jamison and our laboratory have described high levels of diastereoselectivity in macrocyclizations utilizing chirality adjacent to the aldehyde or alkyne.<sup>4</sup> The Jamison approach to amphidinolides T1 and T4 in particular described a detailed conformational analysis of the diastereoselectivity of macrocyclizations of aromatic alkynes.<sup>4c</sup> To more fully explore the potential of diastereoselective macrocyclizations, including those potentially involving long-range diastereoselectivity, we examined the reactivity of ynals **9a–9f** (Scheme 3). Interestingly, the 11-membered macrocycles **10a–10c** were all formed as single diastereomers. Remarkably, despite the remote positioning of substituents, macrocycle **10d** was generated with a high level of 1,5-diastereocontrol (90:10).

The stereochemistry of **10a–10c** was deduced by COSY and NOE experiments. The diol derived from **10d**, by removing the two triisopropylsilyl groups, was crystalline, and its structure was unambiguously assigned by X-ray crystallography.<sup>8</sup> Further study showed that the diastereoselectivity of the macrocyclization

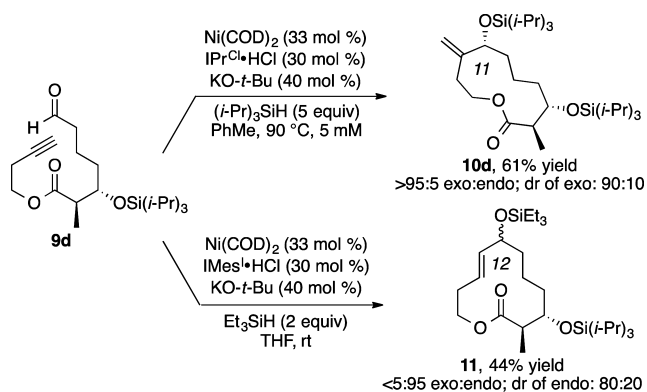
Scheme 3. Diastereoselectivity Study<sup>a</sup>

<sup>a</sup>rr is the ratio of regioisomers. <sup>b</sup>Combined yield.

strongly depends on the ring size formed. With a methyl substituent at the homopropargylic position, 13- and 16-membered macrocycles **10e** and **10f** were synthesized in good yields employing the standard conditions. Compared to the 11-membered macrocycle **10b** (dr >95:5), the diastereoselectivity of 13-membered macrocycle **10e** dropped to 76:24, and a completely nonselective reaction was observed for the synthesis of 16-membered macrocycle **10f** (dr 50:50).

Coupled with the previously reported advances allowing endoselective macrocyclizations of terminal alkynes,<sup>4b</sup> the exocyclization protocol described herein now allows either regioisomer to be effectively obtained from a common substrate. To demonstrate the versatility of this feature, substrate **9d** was subjected to the macrocyclization conditions, allowing either endo- or exocyclization to proceed (Scheme 4). Whereas the

## Scheme 4. Regiochemical Alterations

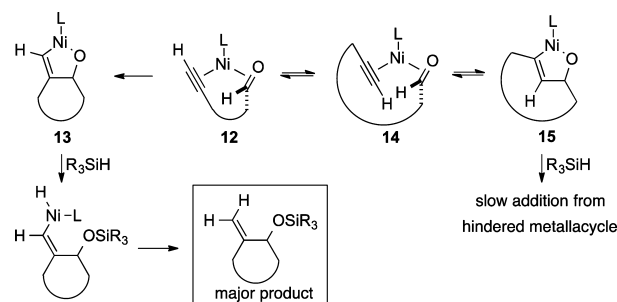


exocyclization procedure requires a bulky ligand  $\text{IPr}^{\text{Cl}}$  and bulky silane  $(i\text{-Pr})_3\text{SiH}$  to produce **10d**, the endocyclization proceeds best with IMes as the ligand and  $\text{Et}_3\text{SiH}$  as the reductant to produce 12-membered macrocycle **11**.

Recent mechanistic investigations of intermolecular nickel-catalyzed reductive couplings have elucidated the operative mechanistic pathways according to the catalyst and silane

structure. The typical pathway for silane-mediated reductive couplings involves rate-determining formation of a nickel metallacycle, which thus governs the regioselectivity of the process.<sup>9</sup> Alternatively, the specific combination of a large NHC ligand, a bulky silane, and high temperature was observed to follow a different kinetic description, where formation of the metallacycle leading to the minor product is reversible.<sup>5a</sup> This outcome leads to very high regioselectivity for the product that possesses the more hindered C–C bond. The conditions (large ligand, bulky silane, high temperature, slow addition) favoring formation of the more hindered exocyclization-derived macrocyclization products (Schemes 2–3) closely pattern the conditions that favored reversible formation of the metallacycle in our recent mechanistic investigations. On this basis, it is likely that the procedure reported herein involves reversible formation of the endocyclic metallacycle **15**, but due to the more hindered nature of the Ni–C bond, its capture by the bulky silane [i.e.,  $(i\text{-Pr})_3\text{SiH}$ ] is inefficient (Scheme 5). Reversion back to the Ni(0)

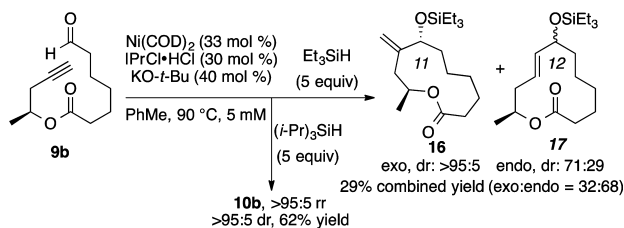
## Scheme 5. Mechanistic Rationale



ynal complex **14**, reorientation of the alkyne to intermediate **12**, and then formation of exocyclic metallacycle **13** allows a productive  $\sigma$ -bond metathesis leading to the preferred formation of the exocyclic product.

According to the above mechanistic hypothesis, the regioselectivity for the exocyclic product should erode as the silane steric hindrance decreases. To address this question, the macrocyclization of ynal **9b** was conducted with  $(i\text{-Pr})_3\text{SiH}$  and also with  $\text{Et}_3\text{SiH}$  under otherwise identical conditions (Scheme 6). Compared to the highly regioselective synthesis of **10b** using

## Scheme 6. Influence of Silane Sterics on Regioselectivity



$(i\text{-Pr})_3\text{SiH}$ , the reaction of **9b** with  $\text{Et}_3\text{SiH}$  generated the products as a mixture of exo- and endocyclization products **16** and **17** with a ratio of 32:68 favoring macrocycle **17** derived from endocyclization. These results support the above hypothesis for the origin of regiocontrol since the use of a smaller silane promotes a faster addition of silane to the hindered endocyclic metallacycle **15**, thus rendering the production of endocyclic products more efficient.

Whereas exocyclization products **10b** or **16** were obtained with high levels of diastereoselectivity regardless of silane



structure, modest levels of diastereocontrol were observed for the endocyclization product **17** (Scheme 6). The choice of silane reducing agents is thus important for the reaction to achieve high regioselectivity (exo vs endo) but has negligible influences on the diastereoselectivity. The diastereoselectivity of the exocyclization reaction is likely controlled by transannular interactions associated with the **12** to **13** transformation. As demonstrated across varying ring sizes, the impact of these interactions, and their resulting influence on diastereoselectivity, strongly depends on the size of the macrocyclic ring formed (Scheme 3, compounds **10b**, **10e**, and **10f**).

In conclusion, a general protocol for the exo-selective macrocyclization of ynals has been developed. By employing a Ni/IPr<sup>Cl</sup> catalyst system paired with (*i*-Pr)<sub>3</sub>SiH as the reducing agent, high selectivity for the synthesis of exoalkylidene macrocycles was achieved. Although IPr<sup>Cl</sup> has been successfully applied to other chemical transformations,<sup>7</sup> its use in reductive coupling reactions of this type has not been previously described. Under the optimized conditions, 10- to 21-membered macrocycles were prepared in synthetically useful yields with high regioselectivity. Complementary to previously published endo-selective macrocyclizations, this study provides access to exoalkylidene macrocycles with high selectivity from similar ynal substrates. Excellent diastereoselectivity of the exo-selective macrocyclization was also observed for macrocycles of certain ring sizes. High levels of diastereocontrol were obtained for macrocycles with substituents quite remote from the reacting alkyne and aldehyde functional groups. Future efforts will involve increasingly complex illustrations of this macrocyclization method and utilization of the novel structures obtained in enzymatic oxidation processes.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic details, spectral data, and CIF file for the X-ray crystallographic data. These materials are available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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