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Synthesis of *N*-Alkenyl 2-Pyridonyl Ethers via a Au(I)-Catalyzed Rearrangement of 2-Propargyloxypyridines

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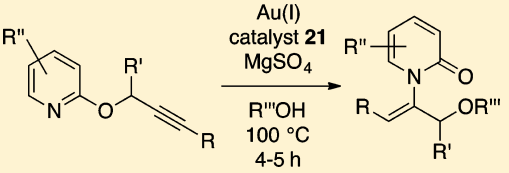
Supporting Information

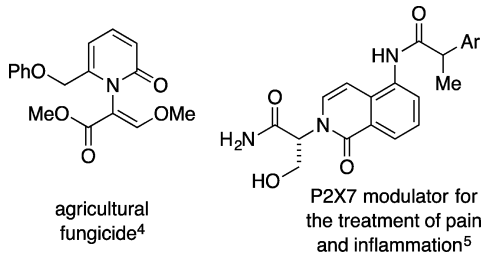
ABSTRACT: *N*-Alkyl 2-pyridones and other enolizable heterocycles are important synthetic constructs, due to their prevalence in natural products and pharmaceutical targets and their capacity to serve as models for a number of biological and chemical processes. The disclosed Au(I)-catalyzed reaction utilizes 2-propargyloxypyridines to access *N*-alkylated 2-pyridone products derived from both 5-*exo* and 6-*endo* addition of the nitrogen to the pendent alkyne. Experimental and computational studies suggest that the desired 5-*exo* *N*-alkenyl 2-pyridonyl ethers are formed reversibly in the transformation. After extensive optimization, biaryl Au(I) catalyst **21** was found to overcome the inherent preference for the 6-*endo* pathway and provide the highest combination of 5-*exo* selectivity and yield. Herein, we report the application of this new Au(I)-catalyzed C−N bond formation to the preparation of a variety of *N*-alkenyl 2-pyridonyl ether analogues, which have the potential to serve as an entry point for the synthesis of complex *N*-alkyl 2-pyridone-containing frameworks.



INTRODUCTION

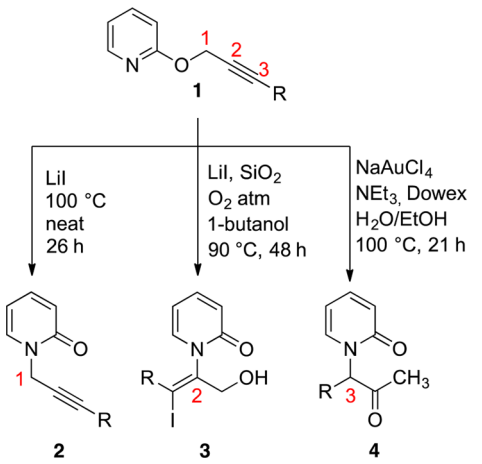
Interest in enolizable heterocycles, such as *N*-alkyl 2-pyridones, stems largely from their ability to serve as a model for hydrogen bonding, tautomerization, and proton shuttling in chemical and biological processes,[1] as well as their prevalence in both natural products[2] and pharmacologically relevant molecules (Scheme 1).[3−5] Access to *N*-alkyl 2-pyridones via direct alkylation of 2-pyridone or 2-hydroxypyridine is complicated by the aromatic nature of the resonance-stabilized anion, leading to both *N*- and *O*-alkylated products.[6] As such, the development of new strategies for the synthesis of *N*-alkylated 2-pyridones and related species, especially as part of functionalized scaffolds, remains an important synthetic goal.

Scheme 1. Biologically Relevant *N*-Alkyl 2-Pyridones



Over the past decade, our laboratory has developed a suite of reactions that accomplish this task, including (1) a lithium iodide promoted alkyl migration for the conversion of 2-alkoxypyridines into *N*-benzyl, *N*-allyl, and *N*-propargyl 2-pyridones **2**;[7] (2) the isolation of *β*-iodo-*N*-alkenyl 2-pyridones **3** from 2-propargyloxypyridines **1** in the presence of lithium iodide and oxygen;[8] and (3) a Au(III)-catalyzed amination−hydration reaction of pyridine **1**, providing *α*-(*N*-2-pyridonyl)-ketones **4** (Scheme 2).[9] These reactions succeed in generating a new C−N bond between the ring nitrogen and either the C1-, C2-, or C3-position of the propargyl side chain. In this way, a single starting material can be used to provide access to a plethora of different synthetic building blocks, each in a single operation. In addition, although compounds **3** and **4** vary markedly in structure, the reactions are presumed to occur via related mechanisms, differing primarily in whether the pendent

Scheme 2. Previously Reported Methods[5−7]



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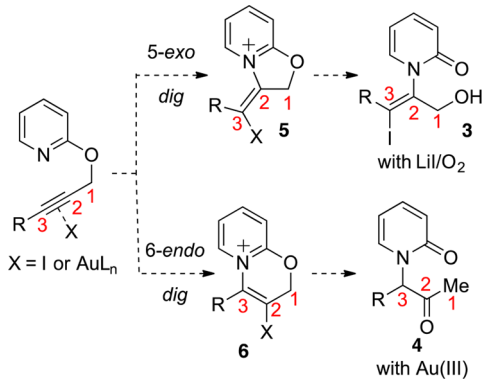
pyridine nitrogen adds to the activated alkyne in a 5-*exo* or 6-*endo* manner (Scheme 3).

Scheme 3. 5-*Exo* and 6-*Endo* Cyclization Manifolds



While each of these methods provides access to a valuable class of compounds, *N*-alkenyl 2-pyridones **3** are of particular interest, as the dense core of orthogonal functionality makes them an attractive entry point to complex *N*-alkyl 2-pyridone-containing scaffolds. However, although alkene **3** is a promising building block, the LiI/oxygen-mediated reaction used for its preparation occurs slowly (48 h) and does not scale well.[6] As such, finding an alternate means of accessing the 5-*exo* reaction manifold, and the resulting *N*-alkenyl 2-pyridones, remains a goal of our laboratory. Utilizing 2-propargyloxypyridines **1** as substrates, efforts have focused on the development of a Au(I)- or Pt(II)-catalyzed 5-*exo* selective C−N bond-forming reaction.[10] This choice stemmed from the ability of these metals to activate alkynes toward addition from an external nucleophile, while simultaneously being electronically unique from Au(III).[11] Herein, we report the achievement of a Au(I)-catalyzed reaction for the synthesis of a range of *N*-alkenyl 2-pyridonyl ethers via the 5-*exo* manifold.

RESULTS AND DISCUSSION

Early efforts to achieve such a reaction targeted the treatment of 2-propargyloxypyridine **7** with AuCl in the presence of an array of additives (e.g., NEt_3, O_2, etc.) (Scheme 4). Under the best AuCl-catalyzed conditions, the reaction was found to be extremely slow, consuming just over half of pyridine **7** after 72 h at 90 °C. However, while sluggish, four unique *N*-alkylated 2-pyridone products were isolated and characterized: allylic ether **8**, derived from 5-*exo* addition of the pyridine nitrogen onto the pendent alkyne; ketone **4** and the related dibutyl ketal **9** and enol ether **10**,[12] all formed through the 6-*endo* process. With the exception of ketone **4**, each of these newly identified compounds incorporates one or more equivalents of the solvent 1-butanol. ^{1}H NMR was utilized to determine the product distribution by analyzing the relative integration of characteristic resonances for the starting material **7** and the four pyridone products, which appear between 3.6 and 5.5 ppm in the crude reaction mixture.[13] In addition, these values could then be utilized to calculate the 5-*exo* selectivity of the reaction (ratio = **8**/(**4** + **9** + **10**)).

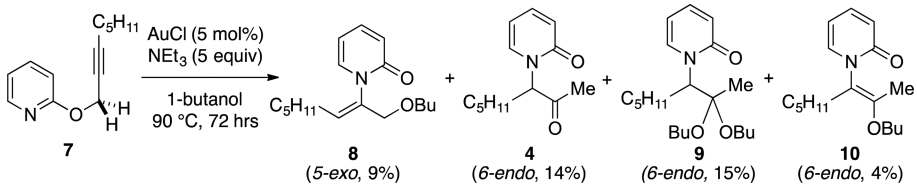
While unselective and inefficient, the AuCl-catalyzed process represents the first instance of the 5-*exo* and 6-*endo* pathways occurring simultaneously in the 2-propargyloxypyridine system. This finding suggests that, while previously observed in isolation, the two reaction modes may be more similar than originally thought. Further, the broad product distribution indicates that Au(I), unlike either LiI or Au(III), is able to access both reaction manifolds. The presence of additional d electrons in Au(I), relative to Au(III), may account for this observation, as Au(I) has the potential to initiate C−O bond scission and formation of carbene **11** that is unlikely for Au(III) (Scheme 5).[14] Subsequent addition of the alcohol nucleophile to the gold-stabilized carbene **11** is then proposed to lead to the observed 5-*exo* product **8** after protodeauration, possibly via auroiminium ion **13**.[15]

Given the potential for reversibility in these pathways, the relative thermodynamic stability of allylic ether **8** and ketone **4** became important. Subjecting pure ether **8** to AuCl in the presence of NEt_3 resulted in no reaction after 72 h at 90 °C. However, treatment of ether **8** with the more reactive biaryl Au(I) catalyst **15** led to the quantitative formation of ketone **4** after only 1 h at 120 °C, suggesting that *N*-alkenyl 2-pyridonyl ether **8** may be formed reversibly under these conditions (Scheme 6).

Computational studies of truncated 2-propargyloxypyridine **16** and the two related products **17** and **18**, conducted at both the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) and M06-2X/6-311+G(2d,p)//M06-2X/6-31G(d) levels of theory, lend additional support for the thermodynamic stability of ketone **4** (Scheme 7).[16] Due to the differences in molecular formula between the starting pyridine **16** and the products, the relative stabilities of allylic ether **17** and ketone **18** were calculated as the free energy change of reaction (ΔG_{rxn}) of pyridine **16** and either methanol or water, respectively. Methanol serves as a simple surrogate for 1-butanol, which is incorporated into ether **8** under the experimental reaction conditions. Using these constraints, ketone **18** was found to be more thermodynamically stable than allylic ether **17** in the ground state by 14.9 and 13.3 kcal/mol (ΔG_{calc}) at the B3LYP and M06-2X levels of theory, respectively. These results are consistent with ketone **18** and the 6-*endo* addition pathway serving as the thermodynamic sink for the process.

Optimization. With this knowledge in hand, initial efforts focused on the identification of a more active Au(I) source that would improve efficiency, allowing for the reaction temperature to be minimized and thus, ideally, for 5-*exo* selectivity to be improved (Table 1). While changing from AuCl to $Au(PPh_3)Cl$ in the presence of AgOTf increased the conversion rate to 77%

Scheme 4. Formation of 2-Pyridones 4, 8, 9, and 10



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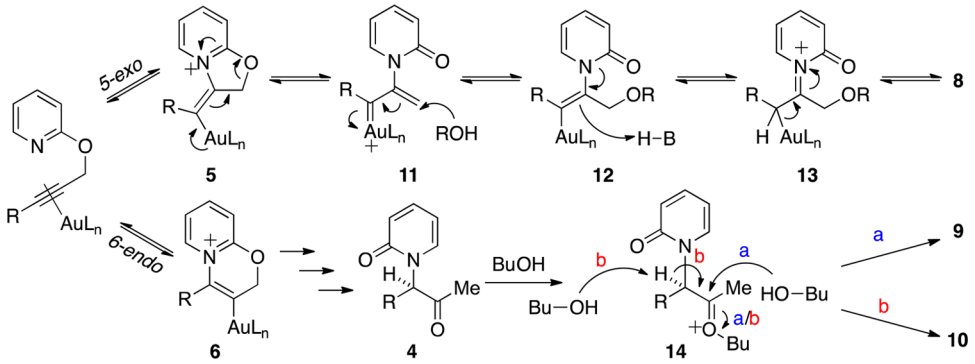
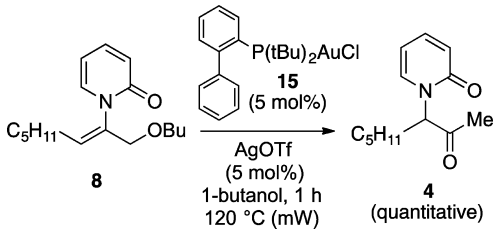
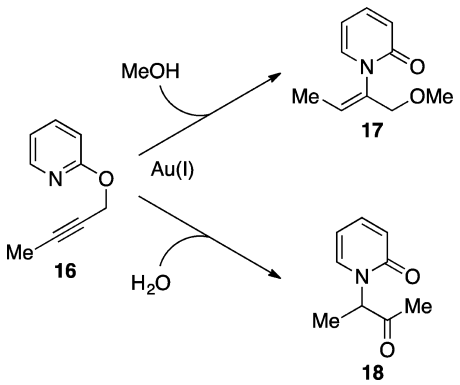
Scheme 5. Proposed Mechanisms



Scheme 6. Relative Stability



Scheme 7. Computational Model System



after 72 h, the most significant gains were realized upon switching to microwave heating, where the reaction proceeded almost to completion in only 75 min at 165 °C (entries 1−3). In this case, higher conversion rates were coupled with a slight improvement in selectivity, although the 6-*endo* pathway continued to be highly preferred. Changing to biaryl catalyst **15**, again in the presence of AgOTf, enhanced the reactivity further, allowing the temperature to be reduced to 120 °C, while maintaining the selectivity and achieving complete consumption of starting material **7** in 1 h (entry 4). At this point, it was also found that a variety of different silver salts could activate Au(I) catalyst **15** (entries 4−7); however, the selectivity ratio was highest when the counterion was either triflate or triflamide (entries 4 and 5).

Utilizing 5 mol % of both catalyst **15** and AgOTf at 120 °C for 1 h in 1-butanol as standard conditions, pyridine **7** was then subjected to the reaction in the presence of further additives (entries 8−14). Treatment with base (e.g., potassium carbonate or proton sponge) was observed to decrease both the efficiency and 5-*exo* selectivity of the reaction (entries 8 and 9), while *p*-toluenesulfonic acid led to complete consumption of starting material **7**, but with high selectivity for the formation of dibutyl ketal **9** (entry 10). In the hope of hindering the formation of 6-*endo* ketone **4**, drying agents were evaluated (entries 11−13). Interestingly, 5-*exo* selectivity was reduced in the presence of either calcium or sodium sulfate, relative to reactions without an additive (entries 11 and 12). Conversely, magnesium sulfate showed a significant enhancement in selectivity (entry 13). Decreasing the temperature to 100 °C allowed for the dominance of 5-*exo* ether **8**, relative to all 6-*endo* products, for the first time (ratio = 1.30, entry 14). It is unclear why magnesium should improve 5-*exo* selectivity compared to other cations, although the sensitivity of the reaction to the presence of ions in solution was also noted above with regards to the counterions of silver salts (entries 4−7).

Given the importance of magnesium sulfate, other catalysts were then screened in its presence (Table 2, Figure 1). Thinking that additional steric bulk might further improve selectivity, we evaluated methoxy-substituted biaryl catalysts **19** and **20** in the presence of AgOTf; however, lower 5-*exo* selectivity was observed relative to the unsubstituted analogue in both cases (entries 1−3). Switching from chloride catalyst **15** to preactivated catalyst **21** in the absence of AgOTf demonstrated that the role of the silver salt was to extract a chloride ion rather than serving as a cocatalyst in the system (entries 1 and 4). In this case, improved selectivity and efficiency were achieved, suggesting that the presence of silver and chloride ions may be detrimental to these features. Additional catalyst classes were also unsuccessful in improving the selectivity ratio, with *N*-heterocyclic carbene catalyst **22** failing to catalyze the reaction to any appreciable extent (entry 5). Pt(II) catalysts were also screened and found to provide efficiency similar to that of catalyst **21**, although the formation of 6-*endo* products was favored (entries 6 and 7). Given these results, catalyst **21**, in the absence of any silver salt, was utilized for all further studies. Additionally, it was discovered that, under these conditions, the reaction occurred equally well when heated either in the microwave reactor or conventionally. This flexibility allows the reaction to be scaled easily with conventional heating without any decrease in yield or 5-*exo* selectivity.

Substrate Scope. Under the optimized reaction conditions, a variety of substituted 2-propargyloxypyridines **25** were subjected to the Au(I)-catalyzed rearrangement (Table 3). The reactions were heated conventionally for 5 h to ensure complete reactivity across the substrate range. Alkyl side chains, including the sterically bulky cyclohexyl group, were generally well-tolerated, allowing *N*-alkenyl 2-pyridonyl ethers **8a** and **26a**,**b** to be isolated in 43−50% yields (entries 1−3). Inclusion of a siloxane group, however, was met with mixed results, as

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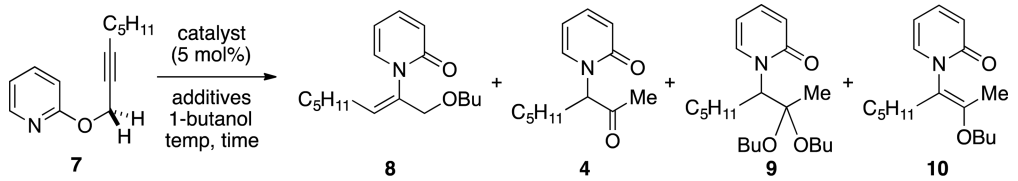
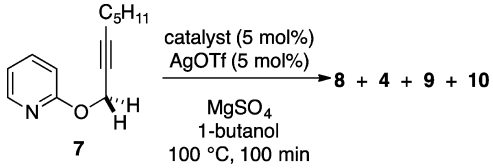
Table 1. Initial Optimization



entry	catalyst (5 mol %)	additives (mol %)	temp (°C)	time (h)	%**8**[a]	%**4**[a]	%**9**[a]	%**10**[a]	ratio[b]
1	AuCl	NEt_3 (500)	90	72	9[c]	14[c]	15[c]	4[c]	0.27
2	$Au(PPh_3)Cl$	AgOTf (5)	80	72	18	13	39	7	0.31
3	$Au(PPh_3)Cl$	AgOTf (5)	165[d]	1.25	32	22	25	14	0.52
4	**15**	AgOTf (5)	120[d]	1	39	20	24	17	0.64
5	**15**	$AgNTf_2$ (5)	120[d]	1	37	21	26	15	0.60
6	**15**	$AgSbF_6$ (5)	120[d]	1	28	21	26	13	0.47
7	**15**	$AgBF_4$ (5)	120[d]	1	32	19	32	15	0.48
8	**15**	AgOTf (5) K_2CO_3 (100)	120[d]	1	8	28	9	6	0.19
9	**15**	AgOTf (5) proton sponge (100)	120[d]	1	12	40	0	4	0.27
10	**15**	AgOTf (5) TsOH (10)	120[d]	1	11	28	57	4	0.12
11	**15**	AgOTf (5) $CaSO_4$ (100)	120[d]	1	26	31	26	11	0.38
12	**15**	AgOTf (5) Na_2SO_4 (100)	120[d]	1	34	20	29	13	0.55
13	**15**	AgOTf (5) $MgSO_4$ (100)	120[d]	1	39	21	14	12	0.83
14	**15**	AgOTf (5) $MgSO_4$ (100)	100[d]	1.67	52	2	21	17	1.30

[a]Percentages determined from integration of signals in the ^{1}H NMR of the crude reaction mixtures. [b]5-*exo*/6-*endo* ratio = **8**/(**4** + **9** + **10**). [c]Isolated yields. [d]Microwave heating.

Table 2. Evaluation of Additional Catalysts



entry	catalyst	%**8**[a]	%**4**[a]	%**9**[a]	%**10**[a]	ratio[b]
1	**15**	52	2	21	17	1.30
2	**19**	46	5	23	16	1.05
3	**20**	18	1	10	6	1.05
4	**21**[c]	47	2	10	15	1.74
5	**22**	2		1		*d*
6	**23**[c]	49	6	29	16	0.96
7	**24**[c]	48	3	33	16	0.92

[a]Percentages determined from integration of signals in the ^{1}H NMR of the crude reaction mixtures. [b]5-*exo*/6-*endo* ratio = **8**/(**4** + **9** + **10**). [c]No AgOTf. [d]Not calculated due to low conversion.

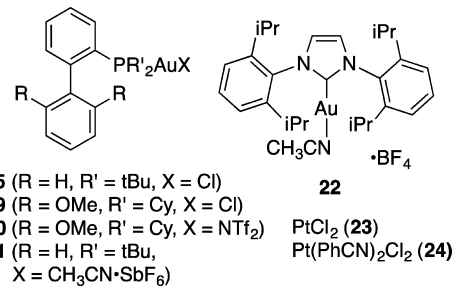


Figure 1. Catalysts screened.

silyl ether **25c** provided the desired *N*-alkenyl 2-pyridone **26c** in 48% yield, while homologue **25d** was recovered from the Au(I) conditions unchanged. Interestingly, a similar trend was observed with silyl substrates **25c** and **25d** in our earlier Au(III) amination−hydration chemistry, in which only pyridine **25c** was reactive.[7] In the case of phenyl-substituted substrate **25e**, none of the desired ether **26e** was observed. Rather, enol ether **27** was isolated in 86% yield as a combination of *E* and *Z* isomers (entry 6 and Figure 2). This stands in contrast to the aliphatic case, in which alkene **10** was isolated as a minor byproduct and occurred as only a single geometric isomer. The aromatic ring adjacent to the methine proton of intermediate **14** (R = Ph) is expected to account for the observed change in both reaction mode and stereoselectivity (Scheme 5).

Extension of the Au(I) rearrangement to the synthesis of more complex ketones and substituted pyridine analogues **25f**–**i** was also explored (Table 3, entries 7–10). Relative to substrates without a propargylic substituent, the rearrangement of *α*-methylated substrate **25f** led to the formation of ketone **26f** in a more moderate 30% yield (entry 7). Conversely, methyl substitution at the 5-position of the pyridine ring led to the highest isolated yield of any allylic ether to date (58%, entry 8). Methyl substitution at either the 3- or the 6-position of the pyridine ring, however, was more problematic, with 3-methyl pyridone **26h** isolated in only 28% yield and no reaction observed for 6-methylpyridine **25i** (entries 9 and 10). These results suggest that substitution in the vicinity of the

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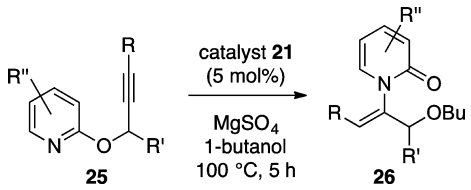
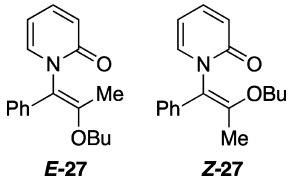
Table 3. Synthesis of *N*-Alkenyl 2-Pyridones 26



25 26

entry	substrate	R	R′	R″	product	yield (%)[a]
1	7	*n*-pentyl	H	H	**8a**	50
2	**25a**	CH_2CH_2Ph	H	H	**26a**	43
3	**25b**	Cy	H	H	**26b**	46
4	**25c**	$(CH_2)_2OTIPS$	H	H	**26c**	48
5	**25d**	CH_2OTIPS	H	H	**26d**	–
6	**25e**	Ph	H	H	**27**	86[b]
7	**25f**	Et	Me	H	**26f**	30
8	**25g**	*n*-pentyl	H	5′-Me	**26g**	58
9	**25h**	*n*-pentyl	H	3′-Me	**26h**	28
10	**25i**	*n*-pentyl	H	6′-Me	**26i**	–

[a]Isolated yields. Mean values from multiple experiments (±2%). [b]Total yield for *E* + *Z* alkene isomers of compound **27**.



E-27 *Z*-27

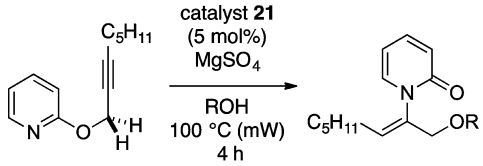
Figure 2. Phenyl enol ether **27**.

heteroatoms likely interferes with metal complexation and thus impedes reaction progress.

As the ether moiety is derived from the solvent, a variety of alcoholic solvents, differing in size and basicity, were also screened in the reaction (Table 4). Across the panel, we were pleased to find that the full range of alcohols could be incorporated into allylic ether products **8**. However, the alcohols were found to differ dramatically in the selectivity and efficiency with which the reaction occurred. Whereas switching from 1-butanol to 3-methyl-1-butanol provided virtually no change in either yield or selectivity (entries 1 and 2), increasing the steric burden nearer to the hydroxyl group had a greater effect. Utilizing isobutyl alcohol as the solvent was found to favor the 6-*endo* rather than 5-*exo* reaction manifold, leading to the isolation of only 22% of isobutyl ether **8c** (ratio = 0.59, entry 3). In contrast, when cyclohexyl alcohol was used, 5-*exo* selectivity improved slightly relative to that of 1-butanol (ratio = 2.57, entry 4). Unfortunately, cyclohexyl ether **8d** is rather unstable, decomposing upon purification, which resulted in a lower than expected 36% isolated yield. It is believed that the decreased stability observed in this case stems from the increased steric demands of the cyclohexyl group in ether **8d**. This assumption is further supported by the absence of ketal **9d** under these conditions.

In the case of the less bulky, but also less basic, benzyl alcohol, the reaction efficiency was reduced, resulting in only 65% of starting material **7** being consumed within 4 h at 100 °C (Table 4, entry 5). However, the 5-*exo* selectivity was good, and enol ether **10e** was absent from the product mixture. Extending the reaction time to 6 h improved the conversion slightly (75%) but led to some erosion in 5-*exo* selectivity (entry 6). The ability to directly form benzyl ether **8e** is advantageous for many applications where a free hydroxyl would be useful; however, isolation of pure ether **8e**, free from ketal **10e**, is difficult.

Table 4. Synthesis of Aliphatic Ethers 8



7 8

entry	R	yield[a] (%)	conv	ratio[b]
1	*n*-Bu (**8a**)	50	100	1.63
2	*i*-pentyl (**8b**)	51	100	1.56
3	*i*-Bu (**8c**)	22	89	0.59
4	Cy (**8d**)	36	82	2.57
5	Bn (**8e**)	41[c]	65	1.95
6	Bn (**8e**)	48[d]	75[e]	1.78

[a]Isolated yields. Mean values from multiple experiments (±2%). [b]5-*exo*/6-*endo* ratio = **8**/(**4** + **9** + **10**). [c]Ether **8e** was isolated as a 2.3:1 mixture with ketal **9e** (R = Bn). [d]Percentage determined from integration of signals in the ^{1}H NMR of the crude reaction mixtures. [e]6 h.

CONCLUSION

The formation of *N*-alkyl 2-pyridone structures derived from both 5-*exo* as well as 6-*endo* cyclization pathways have been shown to occur simultaneously under both Au(I)- and Pt(II)-catalyzed conditions. Further, both experiment and computation suggest that 5-*exo* *N*-alkenyl 2-pyridonyl ether products **8** and **26** are formed reversibly. After extensive optimization, biaryl catalyst **21** was found to overcome the reaction's inherent preference for 6-*endo* reactivity and offer the highest combination of 5-*exo* selectivity and yield. While isolated yields of *N*-alkenyl 2-pyridonyl ethers **8** and **26** remain moderate (12 examples, 22–58% yield), the usefulness of this class of compounds as an entry point for the installation of *N*-alkyl 2-pyridones into a range of complex scaffolds is significant and renders this method an important step toward the inclusion of this motif into targets of interest.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents were purchased from commercial venders and used as received, with the exception of alcoholic solvents, which were distilled from CaH_2 and degassed with argon prior to use. An Anton Paar Monowave 300 microwave reactor with external IR temperature sensing was used for all microwave heating. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer. Chemical shifts are reported in parts per million relative to $CDCl_3$. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); qt (quartet of triplets); app (apparent).

*General Procedure for the Au(I)-Catalyzed Rearrangement. 1-Butoxy-2-(2-pyridonyl)oct-2-ene (**8a**).* Catalyst **21** (19.6 mg, 0.025 mmol), $MgSO_4$ (60 mg, 0.50 mmol), 2-propargyloxypyridine **7** (103 mg, 0.51 mmol), and 1-butanol (2 mL) were added to a G10 microwave vial equipped with a stir bar in an inert atmosphere glovebox. The vial was sealed, removed from the inert environment, and heated at 100 °C in an oil bath. After 5 h, the vial was removed from the bath, and CH_3CN (1 mL) was added and agitated for 1 h. The mixture was then filtered through a cotton plug, rinsed with ethyl acetate (8 mL), and concentrated in vacuo. Purification by column chromatography on Davisil grade SiO_2 (7.5 to 10% ethyl acetate in

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hexanes) provided 71 mg (50%) of **8a** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 6.8 Hz, 1H), 7.23 (d, J = 5.2 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 5.62 (t, J = 8.0 Hz, 1H), 4.22 (s, 1H), 4.05 (s, 1H), 3.61 (sextet, J = 6.4 Hz, 2H), 1.85−1.98 (m, 1H), 1.56−1.74 (m, 3H), 1.30 (sextet, J = 7.6 Hz, 2H), 1.13−1.33 (m, 6H), 0.87 (t, J = 7.6 Hz, 3H), 0.82 (app t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 159.2, 138.6, 134.5, 120.5, 105.4, 85.4, 67.2, 56.6, 31.5, 31.4, 30.7, 25.5, 22.4, 19.3, 13.9, 13.7; IR (neat) 2931, 2868, 1661, 1589 cm^{-1}; HRMS (ESI-TOF) m/z 300.1940 [300.1939 calcd for $C_{17}H_{27}NO_2Na$ (M + Na)$^+$].

*2,2-Dibutoxy-3-(2-pyridonyl)octane (**9**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 6.8 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 6.08 (t, J = 6.8 Hz, 1H), 5.33 (dd, J = 2.8, 12.0 Hz, 1H), 3.45 (app heptet, J = 7.2 Hz, 3H), 3.35 (pentet, J = 7.6 Hz, 1H), 1.85−1.94 (m, 1H), 1.67−1.78 (m, 1H), 1.40−1.54 (m, 4H), 1.06−1.38 (m, 10H), 1.21 (s, 3H), 0.86 (app q, J = 7.6 Hz, 6H), 0.78 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 138.6, 135.7, 120.0, 105.3, 101.6, 62.5, 61.2, 57.3, 32.2, 32.1, 31.5, 27.9, 25.3, 22.4, 19.4, 18.7, 13.9, 13.85, 13.84; IR (neat) 3461, 2956, 2870, 1665, 1591, 1136 cm^{-1}; HRMS (ESI-TOF) m/z 374.2675 [374.2671 calcd for $C_{21}H_{37}NO_3Na$ (M + Na)$^+$].

*(E)-1-Butoxy-2-(2-pyridonyl)oct-2-ene (**10**) (isolated as a 5:1 mixture with ketone **4**; only resonances from **10** reported):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 6.4 Hz, 1H), 6.54 (d, J = 9.2 Hz, 1H), 6.10 (t, J = 6.8 Hz, 1H), 3.76 (t, J = 6.4 Hz, 2H), 2.53−2.65 (m, 1H), 2.27−2.38 (m, 1H), 1.62 (pentet, J = 6.4 Hz, 2H), 1.62 (s, 3H), 1.43 (sextet, J = 7.6 Hz, 2H), 1.15−1.34 (m, 6H), 0.93 (t, J = 7.6 Hz, 3H), 0.82 (app t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 150.2, 139.8, 139.7, 125.5, 122.1, 105.7, 68.4, 32.1, 31.8, 28.1, 26.6, 22.6, 19.4, 14.2, 14.1, 13.2; IR (neat) 3458, 2928, 2865, 1663, 1587, 1534, 1242 cm^{-1}; HRMS (ESI-TOF) m/z 278.2097 [278.2115 calcd for $C_{17}H_{28}NO_2$ (M + H)$^+$].

*1-Butoxy-5-phenyl-2-(2-pyridonyl)pent-2-ene (**26a**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (19.5 mg, 0.025 mmol), $MgSO_4$ (60 mg, 0.50 mmol), 2-propargyloxypyridine **25a** (119 mg, 0.50 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (7.5 to 10% ethyl acetate in hexanes) provided 67 mg (43%) of **26a** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 1H), 7.22−7.28 (m, 1H), 7.14 (app t, J = 6.2 Hz, 3H), 6.53 (d, J = 8.8 Hz, 1H), 6.11 (t, J = 6.4 Hz, 1H), 5.72 (t, J = 7.6 Hz, 1H), 4.28 (d, J = 2.4 Hz, 1H), 4.10 (d, J = 2.4 Hz, 1H), 3.64 (octet, J = 6.0 Hz, 2H), 2.63 (ddd, J = 4.8, 11.2, 13.6 Hz, 1H), 2.50 (ddd, J = 5.6, 10.8, 14.0 Hz, 1H), 2.16−2.30 (m, 1H), 1.97−2.08 (m, 1H), 1.62 (pentet, J = 6.8 Hz, 2H), 1.34 (sextet, J = 7.6 Hz, 2H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 158.8, 141.1, 138.8, 134.4, 128.4, 126.0, 120.5, 105.7, 85.9, 67.3, 56.6, 33.6, 32.4, 30.8, 29.7, 19.3, 13.7; IR (neat) 3465, 3028, 2930, 2870, 1661, 1588, 1536 cm^{-1}; HRMS (ESI-TOF) m/z 312.1932 [312.1958 calcd for $C_{20}H_{26}NO_2$ (M + H)$^+$].

*1-Butoxy-3-cyclohexyl-2-(2-pyridonyl)prop-2-ene (**26b**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (19.5 mg, 0.025 mmol), $MgSO_4$ (60 mg, 0.50 mmol), 2-propargyloxypyridine **25b** (108 mg, 0.50 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (7.5 to 10% ethyl acetate in hexanes) provided 67 mg (46%) of **26b** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 6.51 (d, J = 9.2 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 5.49 (d, J = 11.6 Hz, 1H), 4.30 (s, 1H), 4.01 (s, 1H), 3.62 (t, J = 6.4 Hz, 2H), 1.89 (qt, J = 2.8, 11.2 Hz, 1H), 1.73 (d, J = 10.0 Hz, 2H), 1.53−1.68 (m, 4H), 1.37 (sextet, J = 7.6 Hz, 2H), 0.96−1.31 (m, 4H), 0.91 (t, J = 7.6 Hz, 3H), 0.71−0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 157.8, 138.5, 135.0, 120.4, 105.3, 86.9, 67.2, 61.5, 37.9, 30.8, 30.1, 28.6, 26.1, 25.7, 25.6, 19.4, 13.7; IR (neat) 3465, 2929, 2856, 1661, 1588, 1537, 1290, 1142 cm^{-1}; HRMS (ESI-TOF) m/z 290.2098 [290.2115 calcd for $C_{18}H_{28}NO_2$ (M + H)$^+$].

*1-Butoxy-2-(2-pyridonyl)-5-triisopropylsilyloxypent-2-ene (**26c**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (20.1 mg, 0.026 mmol), $MgSO_4$ (61 mg, 0.51 mmol), 2-propargyloxypyridine **25c** (167 mg, 0.50 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (5 to 7.5% ethyl acetate in hexanes) provided 98 mg (48%) of **26c** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.09 (t, J = 7.6 Hz, 1H), 5.73 (t, J = 8.0 Hz, 1H), 4.25 (d, J = 2.0 Hz, 1H), 4.05 (d, J = 2.0 Hz, 1H), 3.66−3.73 (m, 2H), 3.57−3.65 (m, 3H), 2.21 (sextet, J = 7.6 Hz, 1H), 1.98 (sextet, J = 6.8 Hz, 1H), 1.59 (pentet, J = 6.8 Hz, 2H), 1.33 (sextet, J = 7.6 Hz, 2H), 0.96−1.02 (m, 21H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.7, 138.6, 134.8, 120.6, 105.3, 105.0, 85.5, 67.3, 60.2, 54.1, 34.8, 30.7, 19.3, 17.9, 13.7, 12.9; IR (neat) 2942, 2867, 1664, 1592, 1106 cm^{-1}; HRMS (ESI-TOF) m/z 408.2911 [408.2928 calcd for $C_{23}H_{42}NO_3Si$ (M + H)$^+$].

*(E)-2-Butoxy-1-phenyl-1-(2-pyridonyl)prop-1-ene ((E)-**27**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (20.0 mg, 0.026 mmol), $MgSO_4$ (63 mg, 0.52 mmol), 2-propargyloxypyridine **25e** (108 mg, 0.52 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (10 to 15 to 40 to 50% ethyl acetate in hexanes) provided 87 mg (59%) of (*E*)-**27** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.33 (m, 5H), 7.17−7.23 (m, 2H), 7.54 (d, J = 9.6 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 3.78 (septet, J = 6.4 Hz, 2H), 2.09 (s, 3H), 1.47 (pentet, J = 6.4 Hz, 2H), 1.21 (sextet, J = 7.6 Hz, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 150.6, 139.9, 139.4, 136.1, 129.1, 128.2, 127.3, 121.8, 121.1, 105.3, 68.2, 31.7, 18.9, 15.1, 13.7; IR (neat) 3447, 3171, 2957, 2873, 1662, 1590, 1247 cm^{-1}; HRMS (ESI-TOF) m/z 284.1641 [284.1645 calcd for $C_{18}H_{22}NO_2$ (M + H)$^+$].

*(Z)-2-Butoxy-1-phenyl-1-(2-pyridonyl)prop-1-ene ((Z)-**27**):* 40 mg (27%) of (*Z*)-**27** as a white solid; mp 135−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.23 (app t, J = 8.8 Hz, 3H), 7.09−7.13 (m, 2H), 6.63 (d, J = 9.2 Hz, 1H), 6.16 (t, J = 6.8 Hz, 1H), 3.91 (t, J = 6.8 Hz, 2H), 1.84 (s, 3H), 1.66 (pentet, J = 7.6 Hz, 2H), 1.38 (sextet, J = 7.2 Hz, 2H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 162.7, 153.5, 139.9, 139.8, 128.0, 127.2, 126.6, 122.2, 106.2, 105.0, 68.6, 31.8, 19.1, 14.7, 13.8; IR (neat) 3172, 2952, 1659, 1592, 1530, 1248 cm^{-1}; HRMS (ESI-TOF) m/z 284.1636 [284.1645 calcd for $C_{18}H_{22}NO_2$ (M + H)$^+$].

*2-Butoxy-3-(2-pyridonyl)hex-3-ene (**26f**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (19.9 mg, 0.026 mmol), $MgSO_4$ (61 mg, 0.51 mmol), 2-propargyloxypyridine **25f** (90 mg, 0.51 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (10 to 15% ethyl acetate in hexanes) provided 38 mg (30%) of **26f** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 6.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 9.2 Hz, 1H), 6.07 (t, J = 6.8 Hz, 1H), 5.93 (t, J = 8.0 Hz, 1H), 4.59 (q, J = 6.8 Hz, 1H), 3.56 (t, J = 6.4 Hz, 2H), 1.85−1.99 (m, 1H), 1.76 (t, J = 7.2 Hz, 1H), 1.71 (d, J = 6.8 Hz, 3H), 1.61 (pentet, J = 6.4 Hz, 2H), 1.37 (sextet, J = 7.6 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H), 0.86 (app t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 151.9, 138.6, 135.4, 120.1, 105.4, 96.7, 66.4, 53.0, 31.1, 24.9, 19.4, 13.8, 11.3, 10.5; IR (neat) 2961, 2867, 1662, 1587, 1536, 1217, 1101 cm^{-1}; HRMS (ESI-TOF) m/z 250.1797 [250.1802 calcd for $C_{15}H_{24}NO_2$ (M + H)$^+$].

*1-Butoxy-2-(5′-methyl-2-pyridonyl)oct-2-ene (**26g**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (19.8 mg, 0.026 mmol), $MgSO_4$ (64 mg, 0.53 mmol), 2-propargyloxypyridine **25g** (110 mg, 0.51 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (7.5 to 10 to 15% ethyl acetate in hexanes) provided 82 mg (58%) of **26g** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.10 (d, J = 9.2 Hz, 1H), 6.46 (d, J = 9.2 Hz, 1H), 5.60 (t, J = 8.0 Hz, 1H), 4.21 (s, 1H), 4.03 (s, 1H), 3.62 (t, J = 6.4 Hz, 2H), 2.02 (s, 3H), 1.83−1.95 (m, 1H), 1.55−1.70 (m, 3H), 1.33 (sextet, J = 7.2 Hz, 2H), 1.13−1.33 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H), 0.70−0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 159.4, 141.2, 131.9, 120.0, 114.2, 85.2,

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67.1, 56.4, 31.5, 31.4, 30.7, 25.6, 22.4, 19.3, 17.3, 13.9, 13.6; IR (neat) 3453, 2931, 2868, 1671, 1601, 1536, 1255 cm^{-1}; HRMS (ESI-TOF) m/z 292.2252 [292.2271 calcd for $C_{18}H_{30}NO_2$ $(M + H)^+$].

*1-Butoxy-2-(3′-methyl-2-pyridonyl)oct-2-ene (**26h**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (20.0 mg, 0.026 mmol), $MgSO_4$ (61 mg, 0.51 mmol), 2-propargyloxypyridine **25h** (110 mg, 0.51 mmol), and 1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (5 to 7.5 to 10% ethyl acetate in hexanes) provided 41 mg (28%) of **26h** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 6.8 Hz, 1H), 7.10 (d, J = 6.4 Hz, 1H), 6.02 (t, J = 6.8 Hz, 1H), 5.63 (t, J = 8.0 Hz, 1H), 4.21 (s, 1H), 4.02 (s, 1H), 3.60 (t, J = 7.2 Hz, 2H), 2.11 (s, 3H), 1.85−1.96 (m, 1H), 1.60−1.72 (m, 1H), 1.59 (pentet, J = 7.2 Hz, 2H), 1.15−1.43 (m, 6H), 1.31 (sextet, J = 7.2 Hz, 2H), 0.86 (t, J = 7.6 Hz, 3H), 0.73−0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.4, 135.9, 131.9, 129.1, 105.0, 85.3, 67.2, 57.0, 31.5, 31.4, 30.7, 25.7, 22.4, 19.3, 17.5, 13.9, 13.7; IR (neat) 3458, 2955, 2868, 1654, 1602, 1559, 1463, 1293, 1185 cm^{-1}; HRMS (ESI-TOF) m/z 292.2256 [292.2271 calcd for $C_{18}H_{30}NO_2$ $(M + H)^+$].

*1-(3-Methylbutoxy)-2-(2-pyridonyl)oct-2-ene (**8b**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (20.2 mg, 0.026 mmol), $MgSO_4$ (60 mg, 0.50 mmol), 2-propargyloxypyridine **7** (102 mg, 0.50 mmol), and 3-methyl-1-butanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C in a microwave reactor for 4 h. Purification by column chromatography on SiO_2 (20 to 40% ethyl acetate in hexanes) provided 78 mg (53%) of **8b** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 6.8 Hz, 1H), 7.22 (t, J = 8.8 Hz, 1H), 6.50 (d, J = 9.2 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 5.62 (t, J = 7.6 Hz, 1H), 4.23 (s, 1H), 4.05 (s, 1H), 3.63 (sextet, J = 6.0 Hz, 2H), 1.84−1.97 (m, 1H), 1.58−1.75 (m, 2H), 1.50 (septet, J = 6.0 Hz, 2H), 1.14−1.34 (m, 6H), 0.84 (t, J = 7.6 Hz, 6H), 0.7−0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 159.3, 138.6, 134.5, 120.5, 105.4, 85.4, 65.9, 56.6, 37.4, 31.5, 31.4, 25.6, 25.1, 22.5, 22.4, 13.9; IR (neat) 2954, 2868, 1663, 1591, 1464, 1140 cm^{-1}; HRMS (ESI-TOF) m/z 292.2251 [292.2271 calcd for $C_{18}H_{30}NO_2$ $(M + H)^+$].

*1-(2-Methylpropoxy)-2-(2-pyridonyl)oct-2-ene (**8c**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (20.3 mg, 0.025 mmol), $MgSO_4$ (63 mg, 0.50 mmol), 2-propargyloxypyridine **7** (103 mg, 0.51 mmol), and 2-methyl-1-propanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 5 h. Purification by column chromatography on Davisil grade SiO_2 (7.5 to 10% ethyl acetate in hexanes) provided 31 mg (22%) of **8c** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 6.8 Hz, 1H), 7.22 (t, J = 6.4 Hz, 1H), 6.51 (d, J = 9.2 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 5.63 (t, J = 7.6 Hz, 1H), 4.22 (s, 1H), 4.03 (s, 1H), 3.41 (t, J = 6.8 Hz, 2H), 3.35 (t, J = 6.8 Hz, 1H), 1.85−1.99 (m, 2H), 1.62−1.75 (m, 1H), 1.15−1.35 (m, 6H), 0.87 (d, J = 6.4 Hz, 6H), 0.78−0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 159.2, 138.6, 134.6, 120.5, 105.4, 85.4, 73.9, 56.7, 31.5, 31.4, 27.9, 25.6, 22.4, 19.2, 13.9; IR (neat) 2957, 2868, 1663, 1589, 1536 cm^{-1}; HRMS (ESI-TOF) m/z 278.2101 [278.2115 calcd for $C_{17}H_{28}NO_2$ $(M + H)^+$].

*1-(Cyclohexoxy)-2-(2-pyridonyl)oct-2-ene (**8d**).* Following the general procedure outlined above for the synthesis of compound **8a**, catalyst **21** (19.3 mg, 0.025 mmol), $MgSO_4$ (60 mg, 0.50 mmol), 2-propargyloxypyridine **7** (99 mg, 0.49 mmol), and cyclohexanol (2 mL) were combined in a G10 microwave vial and heated at 100 °C for 4 h. Purification by column chromatography on SiO_2 (15 to 20% ethyl acetate in hexanes) provided 53 mg (36%) of **8d** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.2 Hz, 1H), 7.21 (app t, J = 7.2 Hz, 1H), 6.50 (d, J = 9.2 Hz, 1H), 6.09 (t, J = 6.8 Hz, 1H), 5.58 (t, J = 7.6 Hz, 1H), 4.28 (s, 1H), 4.02 (s, 1H), 3.90−3.98 (m, 1H), 1.85−1.96 (m, 1H), 1.53−1.84 (m, 5H), 1.14−1.52 (m, 13H), 0.82 (app t, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 157.0, 138.6, 134.7, 120.4, 105.3, 85.7, 74.0, 56.9, 31.5, 31.4, 30.9, 30.6, 25.57, 25.56, 23.3, 22.4, 13.9; IR (neat) 2931, 2862, 1660, 1588, 1536, 1459 cm^{-1}; HRMS (ESI-TOF) m/z 304.2273 [304.2271 calcd for $C_{19}H_{30}NO_2$ $(M + H)^+$].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02075.

Details of 5-*exo*/6-*endo* ratio calculations, computational studies, and ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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