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Synthesis of 1,3-Amino Alcohols, 1,3-Diols, Amines, and Carboxylic Acids from Terminal Alkynes

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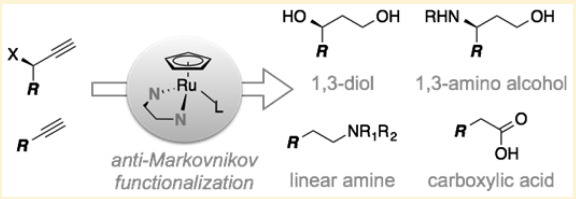
Supporting Information

ABSTRACT: The half-sandwich ruthenium complexes **1**−**3** activate terminal alkynes toward anti-Markovnikov hydration and reductive hydration under mild conditions. These reactions are believed to proceed via addition of water to metal vinylidene intermediates (**4**). The functionalization of propargylic alcohols by metal vinylidene pathways is challenging owing to decomposition of the starting material and catalytic intermediates. Here we show that catalyst **2** can be employed to convert propargylic alcohols to 1,3-diols in high yield and with retention of stereochemistry at the propargylic position. The method is also amenable to propargylic amine derivatives, thereby establishing a route to enantioenriched 1,3-amino alcohol products. We also report the development of formal anti-Markovnikov reductive amination and oxidative hydration reactions to access linear amines and carboxylic acids, respectively, from terminal alkynes. This chemistry expands the scope of products that can be prepared from terminal alkynes by practical and high-yielding metal-catalyzed methods.



INTRODUCTION

Metal-catalyzed additions of heteroatom nucleophiles to alkynes are valuable methods that enable access to aldehydes, ketones, imines, enamides, and enol esters, among other products.[1] Several catalysts have been reported to effect the anti-Markovnikov addition of water to terminal alkynes.[2] Recently, our group developed the half-sandwich ruthenium complexes **1**−**3**, which mediate the anti-Markovnikov hydration of terminal alkynes under mild conditions (Figure 1).[3] When

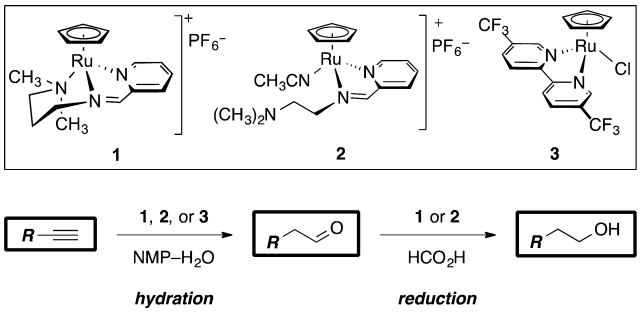
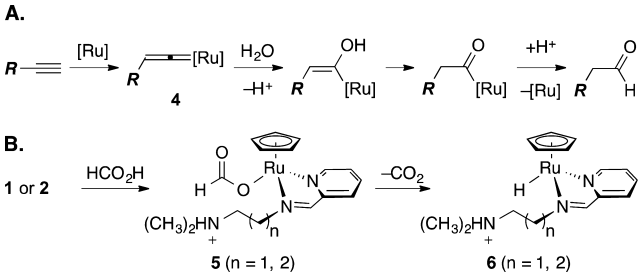


Figure 1. Structures of the catalysts **1**−**3** and the overall sequence for the anti-Markovnikov reductive hydration of alkynes.

catalyst **1** or **2** is used in conjunction with formic acid, the aldehyde intermediate is reduced in situ, to provide linear alcohol products (a reaction we refer to as reductive hydration).[3a,c] High conversions are achieved at ambient temperature within 8−48 h in the presence of 2−10 mol % metal. The catalysts are compatible with a range of functional groups including alkyl halides, esters, carboxylic acids, ketones, alkenes, and alcohols. The connection between unsaturated hydrocarbon starting materials and heteroatom-substituted products established by these catalysts has strategic merit, as these two classes of functional groups display orthogonal reactivity under many conditions.[4]

The specific mechanism of alkyne activation by **1**−**3** is not yet known but may involve the generation of metal vinylidene intermediates (**4**, Scheme 1A).[5] The addition of water, followed

Scheme 1. (A) Proposed Pathway for the Anti-Markovnikov Hydration of Terminal Alkynes by Catalysts 1−3; (B) Pathway for Generation of the Ruthenium Hydride 6 from Catalyst 1 or 2 and Formic Acid



by tautomerization and protonolysis, would complete the hydration step. We provided evidence[3c] that aldehyde hydrogenation by **1** and **2** proceeds via heterolytic activation of formic acid, to generate the ruthenium formate **5** (Scheme 1B). The formate **5** is believed to undergo decarboxylation to the monohydride **6**, which effects outer-sphere reduction[6] of the

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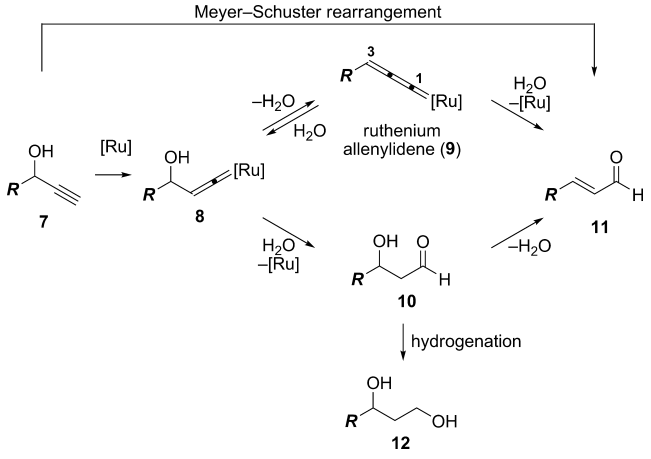
aldehyde. Given the high activity of these catalysts, it was of interest to determine if their substrate scope could be broadened to access other important classes of products. Specifically, the functionalization of propargylic alcohols by pathways involving metal vinylidene species is a challenging problem[7] owing to the instability of the catalytic intermediates (vide infra). These substrates are readily accessible by asymmetric acetylide additions to carbonyl compounds,[8] and their successful transformation would establish a route to 1,3-diol products. In addition, we sought to access other product classes and have developed methods to effect the formal reductive hydroamination and oxidative hydration of alkynes to access linear amines and carboxylic acids, respectively. Collectively, these reactions expand the scope of products that can be formed from terminal alkynes under mild and practical conditions.

RESULTS AND DISCUSSION

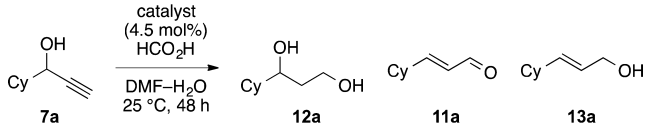
Syntheses of 1,3-Diols and 1,3-Amino Alcohols. The stereoretentive reductive hydration of enantioenriched propargylic amines and alcohols would provide access to 1,3-amino alcohols and 1,3-diols. Although Hintermann, Bolm, and co-workers reported an efficient method for the anti-Markovnikov hydration of propargylic sulfonamides,[9] the anti-Markovnikov hydration of propargylic alcohols is notoriously difficult,[7] and only a handful of examples have been reported. As shown by Wakatsuki and co-workers, propargylic alcohols are converted to α,β-unsaturated aldehydes (**11**) in high yield using classical alkyne hydration catalysts (Scheme 2).[10] These may form by in situ dehydration of the β-hydroxyaldehyde **10** or by a Meyer–Schuster rearrangement.[11] An additional complication arises from the reversible dehydration of 3-hydroxy vinylidene intermediates **8** to form allenylidene complexes **9**,[12] which abolishes the stereochemistry of the starting material. This facile mode of reactivity has been leveraged toward the development of metal-catalyzed substitution reactions of propargylic alcohols.[13] Addition of water to the C-1 position of the allenylidene **9** constitutes an additional route to the unsaturated aldehyde **11**.

Scheme 2. Potential Reaction Pathways in the Anti-Markovnikov Reductive Hydration of Propargylic Alcohols

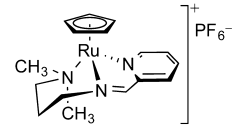
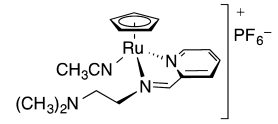
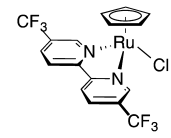


We posited that a general reductive hydration of propargylic alcohols may be realized if the hydration and hydrogenation could be conducted at or below ambient temperature and if the residence time of the β-functionalized aldehyde intermediate could be suppressed. Our previous studies established that the rate of decarboxylation of formic acid to provide the key monohydride intermediate **6** is faster using the κ^2-complex **2** than using the κ^3-complex **1**.[3c] This suggested that complex **2** may provide higher selectivity for the desired 1,3-diol product **12** through an increased rate of reduction of the aldehyde intermediate. To test this hypothesis, the reductive hydration of 1-cyclohexylprop-2-yn-1-ol (**7a**) was evaluated using 4.5 mol % of **1**, **2**, or **3** and 4 equiv of formic acid in aqueous *N*,*N*-dimethylformamide (DMF) at 25 °C (Table 1). The κ^3-complex **1** provided 1-cyclohexylpropane-1,3-diol (**12a**) in 36% yield, along with 23% of (*E*)-3-cyclohexylacrylaldehyde (**11a**) and 27% of unreacted **7a**. By comparison, the κ^2-complex **2** provided an 80% yield of the desired 1,3-diol **12a**. Although the unsaturated aldehyde **11a** was not observed when catalyst **2** was employed, (*E*)-3-cyclohexylprop-2-en-1-ol (**13a**) was formed in 17% yield. A control experiment demonstrated that **13a** is generated by 1,2-reduction of **11a**. In accord with our hypothesis, the ratio of product **12a** to undesired rearranged products **11a** and **13a** is higher using complex **2** than with complex **1**. The bipyridine ruthenium complex **3**, which displays negligible hydrogenation activity at ambient temperature, provided the unsaturated aldehyde **11a** in 84% yield, demonstrating the instability of the β-hydroxyaldehyde **10a** under the conditions of the reductive hydration.

Table 1. Reductive Hydration of 1-Cyclohexylprop-2-yn-1-ol (7a) Using Catalysts 1, 2, or 3[a]



7a **12a** **11a** **13a**

entry	catalyst	yield[b] 12a	11a	13a	12a: (11a+13a)
1	 **1**	36%	23%	<1%	1.6:1
2[c]	 **2**	80%	<1%	17%	4.7:1
3	 **3**	<1%	84%	<1%	–

[a]All reactions were conducted on a 250 μmol scale and employed 4.5 mol % of **1**, **2**, or **3** and 4 equiv of formic acid. [b]Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c]**2** was prepared in situ from $[CpRu(CH_3CN)_3]PF_6$ and the iminopyridine ligand; see the Experimental Section.

It was deemed valuable from a practical standpoint to develop the reductive hydration of *C*-trimethylsilyl propargylic alcohols, as these can be formed from the addition of the liquid reagent trimethylsilylacetylene (as opposed to gaseous acetylene itself) to an aldehyde. We have previously shown that silylalkynes undergo a desilylation–reductive hydration

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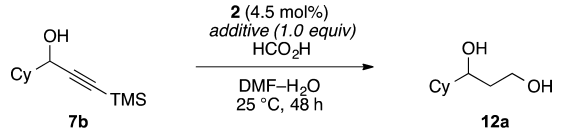
sequence at 55 °C.[3a] To conduct the reaction at ambient temperature, we evaluated the ability of various reagents to promote the desilylation of 1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-ol (**7b**) under the conditions of the reductive hydration reaction (Table 2). In the absence of any additive, a 57% yield

Table 2. Optimization of the Desilylative Reductive Hydration of 1-Cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-ol (7b)[a]



entry	additive	yield **12a**[b]	conv. **7b**[b]
1	none	57%	66%
2	AcOH	60%	69%
3	CH_3OH	59%	68%
4	H_3PO_4	40%	63%
5	HCl (1 N aqueous)	0%	0%
6	TBAF	57%	80%
7[c]	*TBAF*	*79%*	*>99%*

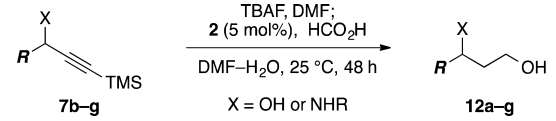
[a]All reactions were conducted on a 250 μmol scale and employed 4.5 mol % of **2**, 4 equiv of formic acid, and 1 equiv of additive. [b]Yields and conversion were determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c]**7b** was stirred with TBAF in anhydrous DMF for 30 min before the addition of H_2O, formic acid, and **2**.

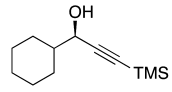
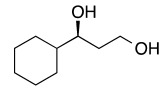
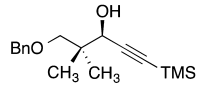
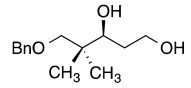
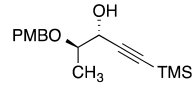
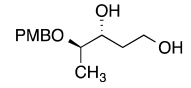
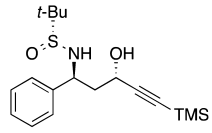
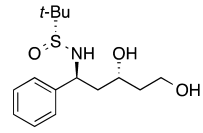
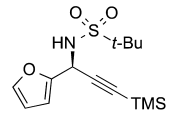
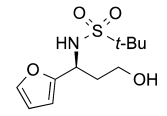
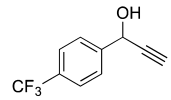
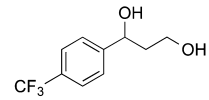
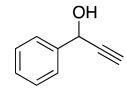
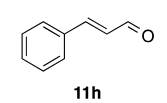
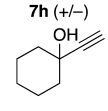
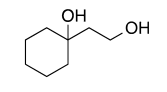
of **12a** was obtained, but the conversion of **7b** was incomplete (entry 1). The addition of acetic acid, methanol, or phosphoric acid, which were expected to promote cleavage of the trialkylsilyl substituent, did not improve the conversion of **7b** (entries 2–4). Aqueous hydrochloric acid impeded the reaction completely, likely due to saturation of the catalyst by excess chloride anion (entry 5). We found that the addition of tetra-*n*-butylammonium fluoride (TBAF) increased the conversion of starting material **7b** to 80%, and 57% of **12a** was obtained (entry 6). It is possible that the TBAF is deactivated by the aqueous formic acid or that the fluoride ion itself reduces the activity of the catalyst. Consequently, we conducted an experiment wherein TBAF was added to starting material **7b** in anhydrous DMF, prior to the addition of water, formic acid, and catalyst **2**. Under these conditions, full conversion of **7b** was observed, and the reductive hydration proceeded smoothly to provide **12a** in 79% yield (entry 7).

Representative *C*-trimethylsilyl propargylic alcohols that undergo the reductive hydration reaction are shown in Table 3. As the configurational stability of the propargylic center was not assured (see discussion above and Scheme 2), the substrates **7b–f** were prepared in stereoisomerically enriched form by asymmetric acetylide addition reactions to the corresponding aldehyde (**7b**, **7c**, and **7d**)[8c,d] or imine (**7f**)[14] derivatives, or by metalloenamine addition to an aldehyde (**7e**).[15]

Each substrate was stirred with TBAF (1 equiv) in anhydrous DMF for 30 min at 25 °C before the addition of water, formic acid, and catalyst **2** (5 mol %). The enantiomeric excess of the propargylic alcohol **7b** was conserved after the reductive hydration, suggesting that allenylidene intermediates (**9**, Scheme 2) are not formed from **7b** and catalyst **2**, and the product was obtained in 77% yield (entry 1). The sterically-hindered enantioenriched alcohol **7c** was also smoothly

Table 3. Scope of the Reductive Hydration of Propargylic Alcohols and Amines[a]



entry	substrate	product	yield[b]
1	 **7b** (99:1 er)	 **12a** (99:1 er)	77%
2	 **7c** (97:3 er)	 **12c** (98:2 er)	71%
3	 **7d** (>20:1 dr)	 **12d** (>20:1 dr)	89%
4[c]	 **7e** (>20:1 dr)	 **12e** (>20:1 dr)	87%
5[c]	 **7f** (97:3 er)	 **12f** (98:2 er)	81%
6	 **7g** (+/–)	 **12g** (+/–)	89%
7	 **7h** (+/–)	 **11h**	22%[d]
8	 **7i**	 **12i**	<1%[d] 69%[e]

[a]All reactions were conducted on a 250 μmol scale and employed 1 equiv of TBAF, 5.0 mol % of **2**, and 4 equiv of formic acid. Entries 6–8 did not employ TBAF. [b]Isolated yields after purification by flash-column chromatography. [c]The deprotection was conducted at 0 °C for 15 min, and 7.0 mol % of **2** was employed. [d]Yield determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [e]Employing 9 mol % of catalyst **1**.[3c]

transformed to the 1,3-diol **12c** with retention of stereochemistry (71%, entry 2). It is noteworthy that the synthesis of **12c** by this approach proceeds in four steps overall and compares favorably with the published six-step sequence.[16] The diastereomerically pure diol **12d** and aminodiol **12e** were obtained in 89% and 87% yields, respectively, from the corresponding propargylic alcohol derivatives (entries 3 and 4, respectively). The arylpropargylic sulfonamide **7f** also underwent high-yielding reductive hydration to provide the amino alcohol **12f** with conservation of stereochemistry (81%, entry 5). In the case of the sulfinamide **7e** and the sulfonamide **7f**, the deprotection step was performed at 0 °C to prevent

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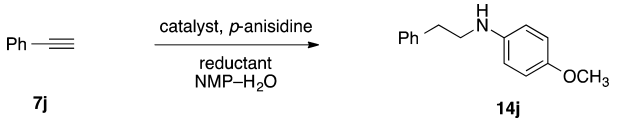
decomposition of the substrate.[17] Interestingly, allylic alcohols (e.g., **13a**, Table 1) were not observed in the reductive hydration of **7b**–**7f**. Instead, ~10–15% of the corresponding terminal alkenes (not shown), presumably formed by hydrogenation of the deprotected alkyne, were observed. Reductive hydration of the electron-deficient benzylic alcohol **7g** proceeded smoothly to provide the 1,3-diol **12g** in 89% yield (entry 6). A limitation of the reaction is seen in the reductive hydration of 1-phenylprop-2-yn-1-ol (**7h**), which provided cinnamaldehyde (**11h**) in 22% yield, along with 73% of **7h** remaining (entry 7). This deviation in product distribution may reflect an increased ease of ionization, which promotes Meyer–Schuster rearrangement[11] or elimination of the β-hydroxy aldehyde intermediate. Tertiary propargylic alcohols such as 1-ethynylcyclohexan-1-ol (**7i**) were unreactive toward **2** (entry 8), but 69% of 1-(2-hydroxyethyl)cyclohexan-1-ol (**12i**) could be obtained when 9 mol % of catalyst **1**[3c] was employed.

Synthesis of Amines. We next sought to develop an anti-Markovnikov reductive hydroamination of terminal alkynes. Although a handful of anti-Markovnikov alkyne hydroamination catalysts have been reported, these require heating to 120 °C under strongly basic conditions,[18] provide variable regioselectivities,[19] or are limited to secondary amine nucleophiles[20] (for anti-Markovnikov alkyne hydroamidation, see ref 21). Several mechanistic possibilities could be envisioned, including trapping of the vinylidene directly by the nitrogen nucleophile or ruthenium-mediated reductive amination[22] of the aldehyde intermediate.

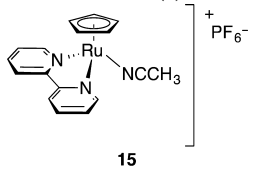
Our studies began with an evaluation of the ability of the ruthenium complexes **1** and **2** to promote the reductive hydroamination of phenylacetylene (**7j**) to form the linear amine **14j** (Table 4). *p*-Anisidine was used as nucleophile because of its low volatility and the ease of removal of the *p*-methoxyphenyl substituent.[23] Unfortunately, the product **14j** was only formed in 17–22% yield, even after prolonged heating at 100 °C in the presence of **1** or **2**, and extensive decomposition of the alkyne was observed (entries 1 and 2). We reasoned that the imine ligands of **1** and **2** may be unstable in the presence of excess *p*-anisidine at high temperature, and so the bipyridine complex **15**[3a] was evaluated. Starting material **7j** was recovered quantitatively after stirring at 25 °C, and a 17% yield of product **14j** was obtained after heating to 100 °C (entries 3 and 4, respectively). Similar results were observed when the more active electron-deficient complex **3** was employed (entry 5). Several potential modes of catalyst deactivation may have been occuring, including displacement of the nitrogen ligands from ruthenium or the accumulation of catalytically inactive intermediates. To probe the latter process, we monitored the reductive hydroamination in entry 2 by UPLC/MS analysis. We observed formation of the iminoacyl complex[24] **16** (Figure 2), but we did not observe product formation even after heating **16** for extended periods. Thus, although complexes **1** and **2** are competent to promote the direct anti-Markovnikov addition of amines to alkynes, catalyst turnover appears to be impeded by the formation of stable iminoacyl complexes that are resistant to protonolysis.

Table 4. Optimization of the Anti-Markovnikov Reductive Hydroamination[a]

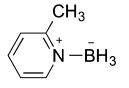


7j 14j

entry	catalyst (mol %)	reductant (equiv)	time, temp	yield 13j[b]	conv. 7j[b]
1	**1** (9)	HCO_2H (4)	72 h, 100 °C	22%	79%
2	**2** (9)	HCO_2H (4)	72 h, 100 °C	17%	67%
3	**15** (9)	HCO_2H (4)	72 h, 25 °C	0%	<1%
4	**15** (9)	HCO_2H (4)	72 h, 100 °C	17%	>99%
5	**3** (9)	HCO_2H (4)	72 h, 100 °C	21%	>99%
6[c]	**3** (2)	PICB (1)	30 h, 25 °C	55%	>99%
7[c]	**3** (2)	PICB (1), AcOH (1)	30 h, 25 °C	69%	>99%

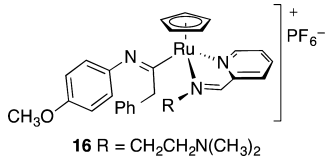


15



2-picoline•borane (PICB)

[a]All reactions were conducted on a 250 μmol scale. [b]Yields were determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c]PICB and AcOH (1 equiv each) were added after 24 h. The reaction was stirred for an additional 6 h.



16 R = $CH_2CH_2N(CH_3)_2$

Figure 2. Structure of the iminoacyl complex **16**.

We reasoned that addition of the amine nucleophile after anti-Markovnikov hydration may provide a means to overcome these challenges.[25] Given that the hydration proceeds at ambient temperature, such a process may deliver a broader substrate scope. 2-Picoline borane (PICB) was chosen as reductant because it has been reported to selectively reduce imines in the presence of aldehydes and ketones under aqueous conditions.[26] In this approach, the substrate would be transformed to an aldehyde by the ruthenium catalyst; addition of a primary amine, followed by PICB-mediated reductive amination, would provide the amine product. The addition of 1 equiv each of PICB and *p*-anisidine directly to a reaction mixture containing the aldehyde derived from **7j** (obtained using 2 mol % **3**) formed the amine **14j** in 55% yield, along with 22% of 2-phenylethanol (entry 6). The addition of acetic acid (1 equiv) suppressed direct reduction of the aldehyde and provided the amine **14j** in 69% yield (entry 7).

Under these conditions a range of alkynes undergo reductive hydroamination with *p*-anisidine as nucleophile at ambient temperature (Table 5). Aromatic alkynes such as **7k** only required 2 mol % ruthenium to complete the hydration step, and the amine **14k** was obtained in 61% yield (entry 1). Somewhat higher loadings of ruthenium (5 mol %) were required to obtain full conversion of aliphatic alkynes. A broad range of functional groups, such as imides (**7m**), esters (**7n**), and alkyl chlorides (**7o**), are compatible with the reaction conditions (67–77% yield of product, entries 3–5, respectively). In addition, we have found that a range of heterocycles are compatible with the hydration and reduction steps. For example, alkynyl furans (**7p**), thiophenes (**7q**), and indoles (**7r**) are efficiently converted to the linear amine products (60–79% yield, entries 6–8). Sterically encumbered alkynes such as 2,4,6-trimethylphenyl (Mes)-acetylene **7s** and the *N*-(*tert*-butox-

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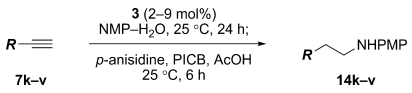
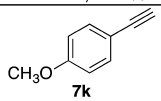
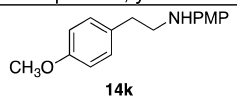
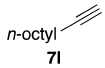
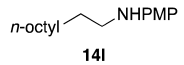
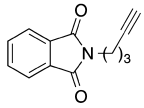
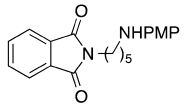
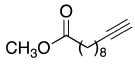
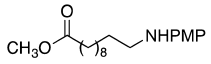
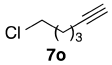
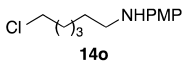
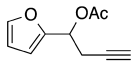
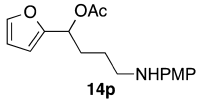
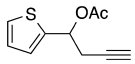
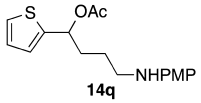
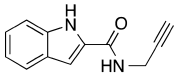
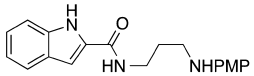
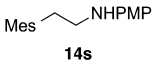
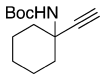
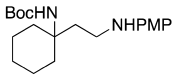
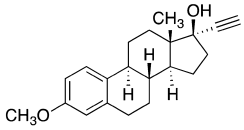
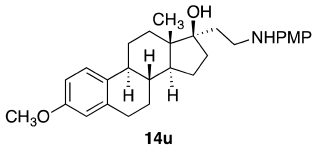
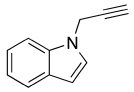
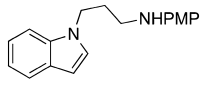
Table 5. Scope of the Anti-Markovnikov Reductive Hydroamination[a]



entry	substrate, mol% **3**	product, yield[b]
1	 **7k** 2 mol%	 **14k** 61%
2	 **7l** 5 mol%	 **14l** 83%
3	 **7m** 5 mol%	 **14m** 77%
4	 **7n** 5 mo%	 **14n** 69%
5	 **7o** 5 mol%	 **14o** 67%
6	 **7p** 5 mol%	 **14p** 79%
7	 **7q** 5 mol%	 **14q** 73%
8[c]	 **7r** 5 mol%	 **14r** 60%
9	 **7s** 7 mol%	 **14s** 86%
10	 **7t** 7 mol%	 **14t** 72%
11	 **7u** 9 mol%	 **14u** 81%
12[d]	 **7v** 9 mol%	 **14v** 73%

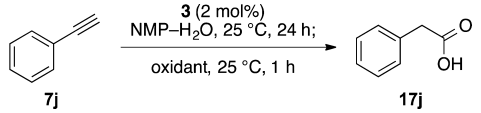
[a]All reactions were conducted on a 250 μmol scale and employed **3**, AcOH (1.1 equiv), *p*-anisidine (1.0 equiv), and PICB (1.0 equiv). [b]Isolated yield after purification by flash-column chromatography. [c]Hydration step conducted for 36 h. [d]Hydration step conducted for 48 h.

ycarbonyl)-protected propargylic amine **7t** required 7 mol % catalyst loading to achieve complete conversion in the hydration step (86% and 72% yield of amine, entries 9 and 10, respectively). The tertiary propargylic alcohol **7u** and the electron-rich indole **7v** were converted to the amines **14u** and **14v** in 81% and 73% yields, respectively (entries 11, 12). Additional experiments revealed that the reaction is also compatible with other primary and secondary aryl and alkyl amines (see Table S1 in Supporting Information), although the efficiency of the reaction was lower.

Synthesis of Carboxylic Acids. The oxidation of organic compounds by ruthenium tetroxide was first introduced by Djerassi and Engle in 1953.[27] Since that time, several protocols employing substoichiometric quantities of ruthenium have been developed to overcome the cost and waste associated with the use of molar equivalents of metal oxidant.[28] We envisioned that we might be able to modify our ruthenium complexes in situ by addition of a suitable oxidant to allow for direct conversion of the hydration product to a carboxylic acid. This two-step, one-flask process would constitute a formal anti-Markovnikov oxidative hydration of terminal alkynes.[29]

To test the feasibility of this approach, we evaluated the hydration of phenylacetylene (**7j**) using 2 mol % of catalyst **3** in aqueous *N*-methyl-2-pyrrolidinone (NMP) at ambient temperature for 24 h, followed by the addition of a terminal oxidant (3 equiv, Table 6). Periodic acid provided a 62% yield of

Table 6. Optimization of the Formal Anti-Markovnikov Oxidative Hydration of Alkynes[a]



entry	oxidant	equiv	yield[b]
1	HIO_4	3.0	62%
2	$NaIO_4$	3.0	>99%
3	NaClO	3.0	<1%
4	$NaBrO_3$	3.0	6%
5	PhIO	3.0	>99%
6	$PhI(OAc)_2$	3.0	>99%
7	$NaIO_4$	1.0	26%
8	PhIO	1.0	48%
9	$PhI(OAc)_2$	1.0	58%

[a]All reactions were conducted on a 300 μmol scale. [b]Yields were determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard.

phenylacetic acid (**17j**) after 1 h (entry 1) while sodium periodate provided a nearly quantitative yield of **17j** (entry 2). Other mildly basic oxidants such as sodium hypochlorite (entry 3) and sodium bromate (entry 4) were ineffective (<1% and 6% yield of **17j**, respectively). Iodosobenzene (entry 5) and bis(acetoxy)iodobenzene (entry 6) were highly effective and provided a nearly quantitative yield of **17j**. The application of stoichiometric amounts of sodium periodate, iodosobenzene, or bis(acetoxy)iodobenzene resulted in lower yields of product (26%–58%, entries 7–9). Attempted oxidation of phenylacetaldehyde using 3 equiv of bis(acetoxy)iodobenzene alone provided only a 16% yield of **17j**, confirming the intermediacy of a ruthenium-based oxidant.[30]

The scope of this formal anti-Markovnikov oxidative hydration is shown in Table 7. Phenylacetylene (**7j**, entry 1),

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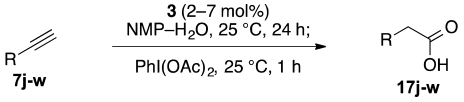
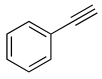
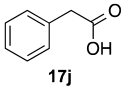
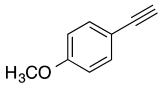
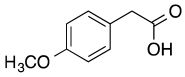
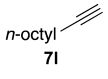
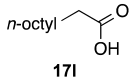
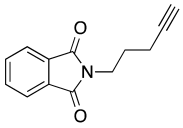
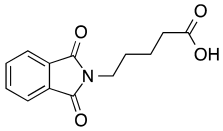
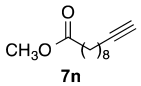
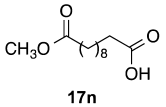
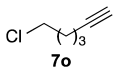
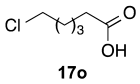
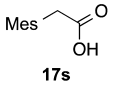
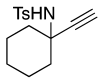
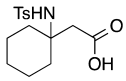
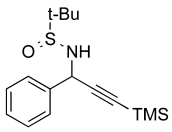
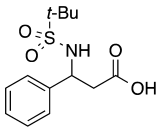
Table 7. Scope of the Two-Step, One-Flask Anti-Markovnikov Oxidative Hydration[a]



entry	substrate	product	mol% **3**	yield (%)[b]
1[c]	 **7j**	 **17j**	2	84%
2[c]	 **7k**	 **17k**	2	82%
3	 **7l**	 **17l**	5	98%
4	 **7m**	 **17m**	5	99%
5	 **7n**	 **17n**	5	94%
6	 **7o**	 **17o**	5	92%
7[d]	 **7s**	 **17s**	7	91%
8[d]	 **7t**	 **17t**	7	91%
9[d,e]	 **7w**	 **17w**	5	80%

[a]All reactions conducted on a 600 μmol scale employing 3.0 equiv $PhI(OAc)_2$. [b]Isolated yields after purification by flash-column chromatography. [c]Employing 2.0 equiv $PhI(OAc)_2$. [d]Employing 4.0 equiv $PhI(OAc)_2$. [e]Hydration conducted at 50 °C.

electron-rich arylalkynes such as 4-methoxyphenylacetylene (**7k**, entry 2), and simple aliphatic alkynes such as 1-decyne (**7l**, entry 3) underwent oxidative hydration in high yield (84%, 82%, and 98%, respectively). A broad range of functional groups are compatible with these conditions. For example, phthalimide- (**7m**, entry 4), ester- (**7n**, entry 5), and primary alkyl chloride- (**7o**, entry 6) containing alkynes underwent oxidative hydration in ≥92% yield. The sterically-hindered alkyne mesitylacetylene (**7s**) was smoothly functionalized to provide the arylacetic acid derivative **17s** in 91% yield (entry 7). Although not extensively investigated, propargylic amine derivatives are also compatible with the reaction conditions. For example, the propargylic sulfonamide **7t** (entry 8) and the propargylic sulfinamide **7w** (entry 9) underwent oxidative hydration to provide the β-amino acid derivatives **17t** and **17w** in 91% and 80% yields, respectively. In the case of sulfinamide **7w**, the first hydration step was conducted at 50 °C to ensure quantitative desilylation and concurrent oxidation of the sulfur atom was observed in the second operation.

CONCLUSION

In this manuscript we have broadened the scope of products that may be prepared from terminal alkynes using catalysts **1**–**3**. We have shown that propargylic alcohols, which have been challenging substrates for anti-Markovnikov functionalization reactions, can be efficiently converted to 1,3-diol products using catalyst **2**. Catalyst **2** also converts propargylic amines to 1,3-amino alcohols in high yield. The efficiencies of these transformations are attributed to the mild conditions of the hydration step and the rapid rate of reduction of the β-functionalized aldehyde intermediates, which conspire to suppress elimination and rearrangement pathways. These reactions proceed without erosion of stereochemistry, thereby providing access to enantioenriched 1,3-difunctionalized products. In addition, we have developed a formal anti-Markovnikov reductive hydroamination reaction that provides access to linear amines and also described a formal anti-Markovnikov oxidative hydration to provide carboxylic acids. These advances significantly expand the utility of this chemistry by increasing the diversity of products that are accessible from alkynes under mild conditions.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with Teflon-coated stir bars and rubber septa, or borosilicate vials, under an atmosphere of nitrogen, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 30–33 °C. Intermediates were purified by flash-column chromatography, as described by Still et al.[31] employing silica gel (60 Å, 40–63 μm particle size) purchased from Sorbent Technologies (Atlanta, GA). Analytical thin-layered chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous potassium permanganate solution ($KMnO_4$) or aqueous bromocresol solution, followed by brief heating on a hot plate (120 °C, 10–15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, *N*,*N*-dimethylformamide, ether, tetrahydrofuran, triethylamine, and toluene were purified according to the method of Pangborn et al.[32] Distilled water, *N*-methyl-2-pyrrolidinone, *N*,*N*-dimethylformamide, and formic acid were deoxygenated by sparging with nitrogen for 30 min before use. Tris(acetonitrile) (η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**S5**),[33] the iminopyridine ligand **S6**,[3c] the tridentate ruthenium complex **1**,[3c] the bidentate ruthenium complex **2**,[3c] the ruthenium chloride complex **3**,[3b] 1-cyclohexylprop-2-yn-1-ol (**7a**),[34] (*R*)-1-cyclohexyl-3-(trimethylsilyl)-2-propyn-1-ol (**7b**),[8c] the aldehyde **S1**,[35] the *t*-butylsulfinyl imine **S3**,[36] (*S*)-*N*-(1-(2-furanyl)-prop-2-yn-1-yl)2-methylpropane-2-sulfonamide (**7f**),[17] α-ethynyl-4-(trifluoromethyl)-benzenemethanol (**7g**),[37] *N*-(2-propyn-1-yl)-1*H*-indole-2-carboxamide (**7r**),[38] 2-ethynyl-1,3,5-trimethylbenzene (**7s**),[3c] *tert*-butyl(1-ethynylcyclohexyl)carbamate (**7t**),[39] 1-(2-propynyl)-1*H*-indole (**7v**),[40] and 2-methyl-*N*-((*R*)-1-phenyl-3-(trimethylsilyl)2-propyn-1-

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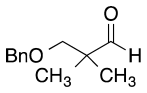
yl)propane-2-sulfinamide (**7w**)[17] were prepared according to published procedures.

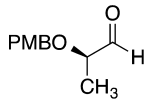
Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400, 500, or 600 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent [$CHCl_3$, δ 7.26; $CHDCl_2$, δ 5.32; C_6H_6, δ 7.16]. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 101, 126, or 151 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0; CD_2Cl_2, δ 54.0). Attached proton test (APT) were recorded at 101 or 151 MHz at 24 °C, unless otherwise noted. ^{13}C NMR and APT data are combined and represented as follows: chemical shift, carbon type [obtained from APT experiments]. Attenuated total reflectance Fourier transform infrared spectra (ATR-FTIR) were obtained using an FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectrometry (HRMS) were obtained using a UPLC/HRMS instrument equipped with a dual API/ESI quadropole high-resolution mass spectrometry detector and photodiode array detector. For clarity, synthetic intermediates not described in the manuscript are numbered in the Experimental Section beginning with **S1**.



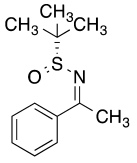
S1

*Synthesis of the Propargylic Alcohol **7c**.* Following the procedure of Carreira and co-workers,[8c] (+)-*N*-methylephedrine (670 mg, 3.74 mmol, 1.20 equiv) and triethylamine (520 μL, 3.74 mmol, 1.20 equiv) were added in sequence to a solution of zinc trifluoromethanesulfonate (1.29 g, 3.54 mmol, 1.10 equiv) in toluene (10 mL) at 25 °C. The resulting solution was stirred for 2 h at 25 °C. Trimethylsilylacetylene (533 μL, 3.74 mmol, 1.20 equiv) was then added via syringe, and the resulting mixture was stirred for 15 min at 25 °C. The aldehyde **S1**[35] (599 mg, 3.12 mmol, 1 equiv) was then added, and the resulting mixture was stirred for 19 h at 25 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (50 mL), and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 5% acetone−pentane) to afford the propargylic alcohol **7c** as a colorless oil (625 mg, 69%): R_f = 0.29 (5% acetone−pentane; UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.52 (q, J = 12 Hz, 2H), 4.20 (d, J = 7.1 Hz, 1H), 3.65 (d, J = 8.8 Hz, 1H), 3.38 (d, J = 7.2 Hz, 1H), 3.29 (d, J = 8.8 Hz, 1H), 1.09 (s, 3H), 0.97 (s, 3H), 0.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (C), 128.6 (CH), 127.9 (CH), 127.7 (CH), 105.6 (C), 90.1 (C), 78.3 (CH_2), 73.8 (CH_2), 71.0 (CH), 39.3 (C), 22.2 (CH_3), 21.2 (CH_3), 0.10 (CH_3). IR (ATR-FTIR), cm^{-1}: 1250 (m), 1060 (m), 1005 (m), 838 (s). HRMS-ESI(m/z): $[M-OH]^+$ calcd for $C_{17}H_{25}OSi^+$, 273.1669; found, 273.1648. Mosher ester analysis[41] of **7c** indicated a 97:3 ratio of enantiomers. The absolute stereochemistry of the major enantiomer was assigned by analogy to that obtained by Carreira and co-workers.[8c]

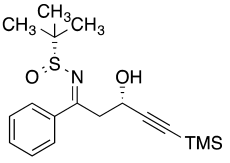
*Synthesis of the Propargylic Alcohol **7d**.* Following the procedure of Marshall and Bourbeau,[8d] a solution of diethylzinc in hexanes (1.0 M, 2.40 mL, 2.40 mmol, 4.80 equiv) was added to a solution of trimethylsilylacetylene (454 μL, 3.21 mmol, 6.40 equiv) in toluene (2.5 mL) at 25 °C. The reaction vessel was fitted with a reflux condenser and then placed in an oil bath that had been preheated to 120 °C. The mixture was stirred and heated for 1 h at 120 °C. The solution was cooled to 25 °C, and the cooled solution was diluted sequentially with ether (6.0 mL) and titanium isopropoxide (178 μL, 601 μmol, 1.20 equiv). The resulting mixture was stirred for 1 h at 25 °C. A solution of aldehyde **S2**[42] (97.4 mg, 501 μmol, 1 equiv) in ether (4.0 mL) was then added. The resulting mixture was stirred for 15 h at 25 °C. The product mixture was diluted with aqueous tartaric acid solution (1.0 M, 10 mL), and the resulting biphasic mixture was stirred for 30 min at 25 °C. The stirred biphasic mixture was transferred to a separatory funnel, and the aqueous layer was extracted with ether (3 × 20 mL). The organic layers were combined, and the combined organic layer was washed with saturated aqueous sodium chloride solution (35 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 20% ether−pentane) to afford the propargyl alcohol **7d** as a white solid (210 mg, 23%, >20:1 dr). ^{1}H NMR spectroscopic data for the propargylic alcohol **7d** prepared in this way were identical to literature values.[43]



S2



S3



S4

*Synthesis of the Propargylic Alcohol **S4**.* Following the procedure of Ellman and co-workers,[15] a solution of *n*-butyllithium in hexanes (2.5 M, 880 μL, 2.20 mmol, 1.10 equiv) was added to a solution of diisopropylamine (336 μL, 2.40 mmol, 1.20 equiv) in tetrahydrofuran (8.3 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. The solution was cooled to −78 °C, and a solution of the *t*-butylsulfinyl imine **S3**[36] (447 mg, 2.00 mmol, 1 equiv) in tetrahydrofuran (4.0 mL) was added dropwise via syringe. The resulting mixture was stirred for 45 min at −78 °C. Zinc bromide (901 mg, 4.00 mmol, 2.00 equiv) and 3-trimethylsilylpropynal (384 μL, 2.60 mmol, 1.30 equiv) were then added in sequence. The resulting mixture was stirred for 3 h at −78 °C. A solution of acetic acid (580 μL, 10.0 mmol, 5.00 equiv) in tetrahydrofuran (5.0 mL) that had been precooled to −78 °C was then added to the cold reaction mixture. The product mixture was diluted with saturated aqueous sodium chloride solution (25 mL), and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layers were combined. The combined organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 60% ether−pentane) to afford the propargyl alcohol **S4** as a yellow oil (900 mg, 56%, >20:1 dr). The relative configuration of **S4** was assigned by analogy to related addition products:[15] R_f = 0.20 (25% ether−pentane; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 7.9 Hz, 2H), 7.53−7.38 (m, 3H), 5.09 (d, J = 9.2 Hz, 1H), 4.49 (m, 1H), 3.76 (t, J = 12.6 Hz, 1H), 3.51 (dd, J = 3.0, 13.2 Hz, 1H), 1.36 (s, 9H), 0.16 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.0 (C), 136.9 (C), 132.2 (CH), 128.9 (CH), 127.7 (CH), 106.3 (C), 88.7 (CH), 59.4 (C), 59.3 (CH), 41.4 (CH_2), 23.3 (CH_3), 0.03 (CH_3). IR (ATR-FTIR), cm^{-1}: 3322 (w, br), 1035 (m), 839 (s). HRMS-ESI(m/z): $[M-OH]^+$ calcd for $C_{18}H_{26}NOSSi^+$, 332.1499; found, 332.1474.

*Syntheses of Amino Alcohol **7e**.* Following the procedure of Ellman and co-workers,[15] a solution of lithium triethylborohydride in tetrahydrofuran (1.0 M, 3.80 mL, 3.77 mmol, 2.50 equiv) was added to a solution of the propargylic alcohol **S4** (528 mg, 1.51 mmol, 1 equiv)

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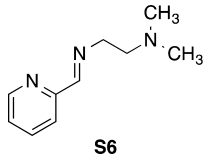
in tetrahydrofuran (2.0 mL) at −78 °C. The resulting solution was stirred for 2 h at −78 °C. The cold product mixture was diluted with saturated aqueous ammonium chloride solution (3.0 mL), and the diluted product mixture was gradually warmed to 25 °C. The warmed product mixture was diluted with saturated aqueous sodium chloride solution (15 mL), and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL), and the organic layers were combined. The combined organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate−pentane) to afford the propargylic alcohol **7e** as a white solid (403 mg, 76%, >20:1 dr). The relative configuration of **7e** was determined by conversion to the corresponding cyclic carbamate, followed by NMR analysis, as previously described:[15] R_f = 0.40 (50% ethyl acetate−pentane; UV, $KMnO_4$). mp 129−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 4.81 (quint, J = 4.8 Hz, 1H), 4.51 (t, br, J = 5.2 Hz, 1H), 4.14 (d, J = 5.1 Hz, 1H), 3.59 (s, 1H), 2.19 (dddd, J = 21.0, 14.4, 7.6, 4.0 Hz, 2H), 1.22 (s, 9H), 0.18 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6 (C), 128.7 (CH), 127.6 (CH), 126.8 (CH), 105.8 (C), 90.6 (C), 60.4 (CH), 56.9 (CH), 55.9 (C), 45.7 (CH_2), 22.8 (CH_3), 0.02 (CH_3). IR (ATR-FTIR), cm^{-1}: 3307 (w, br), 1008 (s), 839 (s), 703 (m). HRMS-ESI(m/z): $[M+H]^+$ calcd for $C_{18}H_{30}NO_2SSi^+$, 352.1761; found, 352.1736.

Synthesis of the Alkyne ***7p****.* A solution of 2-propynylmagnesium bromide in ether[44] (0.90 M, 12.0 mL, 10.8 mmol, 2.16 equiv) was added dropwise via syringe to a solution of furfural (480 mg, 5.00 mmol, 1 equiv) in ether (5.0 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C. The mixture was stirred for 45 min at 25 °C and then was cooled to 0 °C. Acetic anhydride (773 μL, 7.00 mmol, 1.40 equiv) was then added dropwise via syringe. The resulting solution was stirred for 20 min at 0 °C. The cooling bath was removed, and the reaction mixture was stirred for 1 h. The product mixture was cooled to 0 °C, and the cooled product mixture was diluted with saturated aqueous ammonium chloride solution (25 mL). The diluted product mixture was transferred to a separatory funnel and extracted with ether (3 × 15 mL). The organic layers were combined, and the combined layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% dichloromethane−pentane) to afford the alkyne **7p** as an orange oil (747 mg, 84%): R_f = 0.31 (50% methylene chloride−pentane; UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 1.8, 0.9 Hz, 1H), 6.43 (dd, J = 3.2, 0.9 Hz, 1H), 6.36 (dd, J = 3.3, 1.8 Hz, 1H), 5.99 (t, J = 6.9 Hz, 1H), 2.86 (dd, J = 6.9, 2.7 Hz, 2H), 2.09 (s, 3H), 1.99 (t, J = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C), 151.1 (C), 143.0 (CH), 110.5 (CH), 109.3 (CH), 79.0 (C), 70.8 (CH), 66.7 (CH), 23.1 (CH_2), 21.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 3293 (br, m), 1737 (s), 1221 (s), 1013 (m). HRMS-ESI(m/z): $[M-OAc]^+$ calcd for $C_8H_7O^+$, 119.0491; found, 119.0492.

Synthesis of the Alkyne ***7q****.* We followed the procedure above using 2-thiophenecarboxaldehyde (561 mg, 5.00 mmol, 1 equiv). Purification by flash-column chromatography (eluting with 50% dichloromethane−pentane) afforded the alkyne **7q** as a yellow oil (966 mg, 99%): R_f = 0.29 (50% methylene chloride−pentane; UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 6.98 (dd, J = 5.1, 3.6 Hz, 1H), 6.19 (t, J = 6.7 Hz, 1H), 2.84 (dd, J = 6.6, 2.7 Hz, 2H), 2.10 (s, 3H), 2.03 (t, J = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C), 141.6 (C), 126.7 (CH), 126.3 (CH), 125.8 (CH), 79.2 (C), 71.2 (CH), 69.2 (CH), 26.7 (CH_2), 21.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 3289 (br, m), 1735 (s), 1221 (s), 1018 (s). HRMS-ESI(m/z): $[M-OAc]^+$ calcd for $C_8H_7S^+$, 135.0263; found, 135.0259.

Synthesis of the 1,3-Diol ***12a*** *(Table 3, Entry 1).* In a nitrogen-filled drybox, a 4 mL vial equipped with a magnetic stirring bar was charged with the propargylic alcohol **7b** (105 mg, 500 μmol, 1 equiv) and *N*,*N*-dimethylformamide (1.0 mL). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. A



S6

solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 500 μL, 500 μmol, 1.00 equiv) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 30 min at 25 °C. Formic acid (76.0 μL, 2.00 mmol, 4.00 equiv), water (500 μL), and a solution of (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**S5**)[33] and the iminopyridine ligand **S6**[3c] in *N*,*N*-dimethylformamide (25 mM, 1.00 mL, 25.0 μmol, 0.0500 equiv) were then added in sequence with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 48 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous ammonium chloride solution (25 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (3 × 30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 60% ethyl acetate−pentane) to afford product **12a** as a colorless oil (61.2 mg, 77%). ^{1}H NMR spectroscopic data for the diol **12a** prepared in this way were identical to literature values.[45]

Synthesis of the 1,3-Diol ***12c*** *(Table 3, Entry 2).* We followed the procedure for **12a** using the propargylic alcohol **7c** (145 mg, 500 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 60% ether−pentane) afforded the diol **12c** as a white solid (85.0 mg, 71%, 98:2 er). ^{1}H NMR spectroscopic data for the 1,3-diol **12c** prepared in this way were identical to literature values.[16] The enantiomeric excess of **12c** was determined to be 92% by the James method.[46]

Synthesis of the 1,3-Diol ***12d*** *(Table 3, Entry 3).* We followed the procedure for **12a** using the propargylic alcohol **7d** (146 mg, 500 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 60% ether−pentane) afforded the 1,3-diol **12d** as a colorless oil (106 mg, 89%, >20:1 dr): R_f = 0.11 (50% ethyl acetate−pentane; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.6, 2H), 4.50 (dd, J = 69.6, 11.3, 2H), 3.93 (dt, J = 9.7, 3.4 Hz, 1H), 3.84 (t, J = 5.6 Hz, 2H), 3.81 (s, 3H), 3.52 (dq, J = 6.4, 2.7 Hz, 1H), 1.79−1.60 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ159.3 (C), 130.4 (C), 129.4 (CH), 113.9 (CH), 77.3 (CH), 73.3 (CH), 70.5 (CH_2), 61.4 (CH_2), 55.4 (CH_3), 33.8 (CH_2), 14.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 3373 (w, br), 2926 (w, br), 1245 (s), 1030 (s). HRMS-ESI(m/z): $[M + Na]^+$ calcd for $C_{13}H_{20}NaO_4^+$, 263.1254.1434; found, 263.1250.

Synthesis of the 1,3-Diol ***12e*** *(Table 3, Entry 4).* A 4 mL vial equipped with a magnetic stir bar was charged with the propargylic alcohol **7e** (87.9 mg, 250 μmol, 1 equiv) and *N*,*N*-dimethylformamide (500 μL) under an atmosphere of argon. The mixture was cooled to 0 °C, and then a solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 250 μL, 250 μmol, 1.00 equiv) was added dropwise via syringe. The resulting mixture was stirred for 15 min at 0 °C. The vial was transferred to a nitrogen-filled bag, and then formic acid (38.0 μL, 1.00 mmol, 4.00 equiv), water (250 μL), and a solution of (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**S5**) and the iminopyridine ligand **S6** in *N*,*N*-dimethylformamide (35 mM, 500 μL, 17.5 μmol, 0.0700 equiv) were added in sequence. The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 48 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a

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separatory funnel. Aqueous saturated ammonium chloride solution (25 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (3 × 30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% methanol−dichloromethane) to afford the diol **12e** as a white solid (65.0 mg, 87%, >20:1 dr): R_f = 0.16 (5% methanol−methylene chloride; UV). mp 83−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5H), 5.04 (m, br, 1H), 4.73 (dt, J = 8.7, 3.9 Hz, 1H), 4.66 (s, br, 1H), 4.10 (m, 1H), 3.91 (m, 1H), 3.77 (m, 1H), 1.93 (m, 3H), 1.65 (m, 1H), 1.21 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3 (C), 128.6 (CH), 127.4 (CH), 126.9 (CH), 68.2 (CH), 60.9 (CH_2), 56.4 (CH), 55.8 (C), 44.9 (CH_2), 37.9 (CH_2), 22.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 3340 (w, br), 2955 (w), 1034 (s), 699 (m). HRMS-ESI(m/z): $[M + Na]^+$ calcd for $C_{15}H_{25}NNaO_3S^+$, 322.1447; found, 322.1436.

*Synthesis of the Sulfonamide **12f** (Table 3, Entry 5).* We followed the procedure for **12e** using the propargylic alcohol **7f** (78.4 mg, 250 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 50% ether−pentane) afforded the alcohol **12f** as a white solid (53.2 mg, 81%): R_f = 0.31 (50% ethyl acetate−pentane; $KMnO_4$). mp 72−75 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 1.9, 0.8 Hz, 1H), 6.34 (dd, J = 3.3, 1.9 Hz, 1H), 6.24 (d, J = 3.3 Hz, 1H), 4.77 (td, J = 9.2, 4.3 Hz, 1H), 4.52 (d, J = 9.7 Hz, 1H), 3.90 (ddd, J = 11.9, 10.1, 3.2 Hz, 1H), 3.73 (dt, J = 11.8, 4.3 Hz, 1H), 2.37, (s, br, 1H), 2.15 (ddt, J = 14.6, 10.1, 4.6 Hz, 1H), 1.98−1.86 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.3 (C), 142.2 (CH), 110.4 (CH), 106.5 (CH), 60.3 (C), 58.5 (CH_2), 50.2 (CH), 38.7 (CH_2), 24.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 3453 (w, br), 3176 (w, br), 1121 (s), 508 (s). HRMS-ESI(m/z): $[M + Na]^+$ calcd for $C_{11}H_{19}NNaO_4S^+$, 284.0927; found, 284.0903. The enantiomeric excess of the alcohol **12f** was determined to be 96% by chiral stationary-phase HPLC analysis (Chiralpak IA, 10% ethanol−hexane, flow rate 1.0 mL/min, 210 nm).

*Synthesis of the 1,3-Diol **12g** (Table 3, Entry 6).* In a nitrogen-filled drybox, a 4 mL vial equipped with a magnetic stir bar was charged with (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**S5**, 10.9 mg, 25.0 μmol, 0.0500 equiv), the ligand **S6** (4.4 mg, 25.0 μmol, 0.050 equiv), and *N*,*N*-dimethylformamide (2.0 mL). The propargylic alcohol **7g** (100 mg, 500 μmol, 1 equiv) was then added. The vial was sealed with Teflon-lined cap, and the sealed vial was removed from the drybox. Formic acid (76.0 μL, 2.00 mmol, 4.00 equiv) and water (500 μL) were added sequentially with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 48 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous ammonium chloride solution (25 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (3 × 30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 3% methanol−dichloromethane) to afford the 1,3-diol **12g** as white solid (97.5 mg, 89%). ^{1}H NMR spectroscopic data for the diol **12g** prepared in this way were identical to literature values.[47]

*Synthesis of the Unsaturated Aldehyde **11h** (Table 3, Entry 7).* In a nitrogen-filled drybox, a 4 mL vial equipped with a magnetic stir bar was charged with (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**S5**, 5.4 mg, 13 μmol, 0.050 equiv), the ligand **S6** (2.2 mg, 13 μmol, 0.050 equiv), and *N*,*N*-dimethylformamide (1.0 mL). The propargylic alcohol **7h** (33.0 mg, 250 μmol, 1 equiv) was then added. The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Formic acid (38.0 μL, 1.00 mmol, 4.00 equiv) and water (250 μL) were added sequentially with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 48 h at 25 °C. 1,3,5-Trimethoxybenzene (16.9 mg, 100 μmol, 0.402 equiv) was added to the product mixture. An aliquot of this mixture (~100 μL) was removed and diluted with chloroform-d (2.0 mL). The diluted mixture was dried over sodium sulfate, and the dried solution was filtered. The filtrate was transferred to an NMR tube. Analysis by ^{1}H NMR spectroscopy indicated 27% conversion of **7h** and 22% yield of the aldehyde **11h**.[48]

*Synthesis of the 1,3-Diol **12i** (Table 3, Entry 8).* In a nitrogen-filled drybox, a 4 mL vial equipped with a magnetic stir bar was charged with (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**S5**, 5.4 mg, 13 μmol, 0.050 equiv), the ligand **S6** (2.2 mg, 13 μmol, 0.050 equiv), and *N*,*N*-dimethylformamide (1.0 mL). The propargylic alcohol **7i** (31.0 mg, 250 μmol, 1 equiv) was then added. The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Formic acid (38.0 μL, 1.00 mmol, 4.00 equiv) and water (250 μL) were added sequentially with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 48 h at 25 °C. Mesitylene (20.0 μL, 144 μmol, 0.575 equiv) was added to the product mixture. An aliquot of this mixture (~100 μL) was removed and diluted with chloroform-d (2.0 mL). The diluted mixture was dried over sodium sulfate, and the dried solution was filtered. The filtrate was transferred to an NMR tube. Analysis of the mixture by ^{1}H NMR spectroscopy indicated 9% conversion of the starting material **7i**. The 1,3-diol product **12i** could not be detected.

*Synthesis of the Amine **14j** (Table 4, Entry 7).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (3.0 mg, 6.0 μmol, 0.020 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and phenylacetylene (**7j**, 30.6 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. 2-Picoline borane (PICB) (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate−pentane) to afford the amine **14j** as a pale yellow oil (47.0 mg, 69%). ^{1}H NMR data for the amine **14j** prepared in this way were in agreement with literature values.[49]

*Synthesis of the Amine **14k** (Table 5, Entry 1).* Following the procedure for **14j** using 4-methoxyphenylacetylene (**7k**, 39.6 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 10% ethyl acetate−pentane) afforded the amine **14k** as a colorless oil (47.0 mg, 61%): R_f = 0.60 (50% ether−pentane; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.32 (t, J = 7.0 Hz, 2H), 2.85 (t, J = 7.0 Hz, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ158.3 (C), 152.3 (C), 142.4 (C), 131.5 (C), 129.9 (CH), 115.0 (CH), 114.5 (CH), 114.1 (CH), 56.0 (CH_3), 55.4 (CH_3), 46.4 (CH_2), 34.8 (CH_2). IR (ATR-FTIR), cm^{-1}: 1507 (s), 1231 (s), 1175 (m), 1031 (s). HRMS-ESI(m/z): $[M + H]^+$ calcd for $C_{16}H_{20}NO_2^+$, 258.1489; found, 258.1483.

*Synthesis of the Amine **14l** (Table 5, Entry 2).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (7.4 mg, 15.0 μmol, 0.050 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and 1-decyne (**7l**, 41.5 mg, 300

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μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. PICB (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added in sequence to the reaction mixture. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether−pentane) to afford product **14l** as a pale yellow oil (65.9 mg, 83%). ^{1}H NMR data for the amine **14l** prepared in this way were in agreement with literature values.[50]

*Synthesis of the Amine **14m** (Table 5, Entry 3).* We followed the procedure for **14l** using *N*-(4-pentynyl)phthalimide (**7m**, 64.0 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 50% ether−pentane) afforded the amine **14m** as a yellow solid (78.6 mg, 77%): R_f = 0.17 (40% ether−pentane; UV). mp 79−81 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.6, 3.1 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 3H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 1.73 (p, *J* = 7.4 Hz, 2H), 1.66 (p, *J* = 7.2 Hz, 2H), 1.45 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6 (C), 152.1 (C), 142.8 (C), 134.1 (CH), 132.3 (C), 123.4 (CH), 115.0 (CH), 114.1 (CH), 56.0 (CH_3), 44.9 (CH_2), 37.9 (CH_2), 29.3 (CH_2), 28.6 (CH_2), 24.6 (CH_2). IR (ATR-FTIR), cm^{-1}: 1707 (s), 1512 (m), 1032 (s), 718(s). HRMS-ESI(*m*/*z*): [M + H]+ calcd for $C_{20}H_{23}N_2O_3^+$, 339.1704; found, 339.1700.

*Synthesis of the Amine **14n** (Table 5, Entry 4).* We followed the procedure for **14l** using methyl undecanoate (**7n**, 58.9 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 60% ether−pentane) afforded the amine **14n** as a white solid (66.3 mg, 69%): R_f = 0.50 (40% ether−pentane; UV). mp 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.5 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 3H), 3.66 (s, 3H), 3.32 (br, 1H), 3.04 (t, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.60−1.54 (m, 4H), 1.42−1.23 (m, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5 (C), 152.1 (C), 143.0 (C), 115.0 (CH), 114.2 (CH), 56.0 (CH_3), 51.6 (CH_3), 45.2 (CH_2), 34.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.3 (CH_2), 25.1 (CH_2). IR (ATR-FTIR), cm^{-1}: 2921 (s), 1518 (s), 1238 (s), 828 (m). HRMS-ESI(*m*/*z*): [M + H]$^+$ calcd for $C_{19}H_{32}NO_3^+$, 322.2377; found, 322.2365.

*Synthesis of the Amine **14o** (Table 5, Entry 5).* We followed the procedure for **14l** using 6-chloro-1-hexyne (**7o**, 35.0 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 20% ether−pentane) afforded the amine **14o** as a pale yellow oil (48.3 mg, 67%): R_f = 0.30 (80% ether−pentane; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H), 3.54 (t, *J* = 6.7 Hz, 2H), 3.07 (t, *J* = 7.1 Hz, 2H), 1.79 (p, *J* = 6.5 Hz, 2H), 1.62 (p, *J* = 7.3 Hz, 2H), 1.53−1.38 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ152.1 (C), 142.9 (C), 115.0 (CH), 114.2 (CH), 56.0 (CH_3), 45.2 (CH_2), 45.0 (CH_2), 32.7 (CH_2), 29.7 (CH_2), 26.9 (CH_2), 26.6 (CH_2). IR (ATR-FTIR), cm^{-1}: 2932 (br, w), 1510 (s), 1251 (br, m), 1027 (m). HRMS-ESI(*m*/*z*): [M + H]$^+$ calcd for $C_{13}H_{21}ClNO^+$, 242.1307; found, 242.1301.

*Synthesis of the Amine **14p** (Table 5, Entry 6).* Following the procedure for **14l** using 1-(2-furanyl)-3-butyn-1-yl acetate (**7p**, 53.5 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 50% ether−pentane) afforded the amine **14p** as a brown oil (66.2 mg, 73%): R_f = 0.20 (30% ether−pentane; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.32 (m, 2H), 5.87 (t, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.09 (t, *J* = 7.1 Hz, 2H), 2.09−2.03 (m, 5H), 1.70−1.51 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4 (C), 152.4 (C), 152.2 (C), 142.6 (CH), 142.5 (C), 115.0 (CH), 114.2 (CH), 110.3 (CH), 108.8 (CH), 68.5 (CH), 55.9 (CH_3), 44.5 (CH_2), 30.2 (CH_2), 25.6 (CH_2), 21.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 1731 (m), 1511 (s), 1227 (s), 1010 (br, m). HRMS-ESI(*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{22}NO_4^+$, 304.1544; found, 304.1512.

*Synthesis of the Amine **14q** (Table 5, Entry 7).* We followed the procedure for **14l** using 1-(2-thiophenyl)but-3-yn-1-yl acetate (**7q**, 58.3 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 50% ether−pentane) afforded the amine **14q** as a brown oil (75.5 mg, 79%): R_f = 0.21 (30% ether−pentane; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.05 (d, *J* = 3.5 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 6.07 (t, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 3.34 (br, 1H), 3.10 (t, *J* = 7.0 Hz, 2H), 2.15−1.95 (m, 5H), 1.73−1.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4 (C), 152.2 (C), 143.3 (C), 142.6 (C), 126.7 (CH), 126.1 (CH), 125.5 (CH), 115.0 (CH), 114.2 (CH), 71.1 (CH), 56.0 (CH_3), 44.6 (CH_2), 34.1 (CH_2), 25.9 (CH_2), 21.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 1730 (m), 1510 (s), 1227 (s), 1017 (br, m). HRMS-ESI(*m*/*z*): [M + H]$^+$ calcd for $C_{17}H_{22}NO_3S^+$, 320.1315; found, 320.1321.

*Synthesis of the Amine **14r** (Table 5, Entry 8).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (7.4 mg, 15 μmol, 0.050 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and *N*-(2-propyn-1-yl)-1*H*-indole-2-carboxamide (**7r**, 59.5 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 36 h at 25 °C. PICB (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added to the reaction mixture in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 70% ether−pentane) to afford product **14r** as a white solid (58.5 mg, 60%): R_f = 0.24 (60% ethyl acetate−pentane; UV). mp 175−180 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (br, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.73 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.59 (br, 1H), 3.75 (s, 3H), 3.63 (q, *J* = 6.3 Hz, 2H), 3.25 (t, *J* = 6.3 Hz, 2H), 2.04 (s, 1H), 1.93 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.7 (C), 152.6 (C), 142.2 (C), 136.2 (C), 130.8 (C), 127.8 (C), 124.5 (CH), 121.9 (CH), 120.7 (CH), 115.0 (CH), 114.7 (CH), 111.8 (CH), 101.7 (CH), 55.8 (CH_3), 42.9 (CH_2), 37.9 (CH_2), 29.1 (CH_2). IR (ATR-FTIR), cm^{-1}: 1643 (s), 1589 (s), 1223 (s), 1022 (s). HRMS-ESI(*m*/*z*): [M + H]$^+$ calcd for $C_{19}H_{22}N_3O_2^+$, 324.1707; found, 324.1700.

*Synthesis of the Amine **14s** (Table 5, Entry 9).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (10.4 mg, 21.0 μmol, 0.0700 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and 2-ethynyl-1,3,5-trimethylbenzene (**7s**, 43.3 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. PICB (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted

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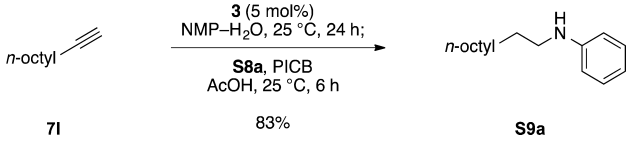
with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether−pentane) to afford product **14s** as a pale yellow oil (69.4 mg, 86%): R_f = 0.57 (33% ether−pentane; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.45 (s, 1H), 3.19 (m, 2H), 2.91 (m, 2H) 2.31 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.3 (C), 142.6 (C), 136.7 (C), 135.8 (C), 132.9 (C), 129.2 (C), 115.1 (CH), 114.2 (CH), 56.0 (CH_3), 44.2 (CH_2), 29.9 (CH_2), 21.0 (CH_3), 20.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 1949 (br, w), 1510 (s), 1231 (s), 817 (s). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{18}H_{24}NO^+$, 270.1853; found, 270.1840.

Synthesis of the Amine ***14t*** *(Table 5, Entry 10).* We followed the procedure for **14s** using *tert*-butyl (1-ethynylcyclohexyl)carbamate (**7t**, 67.0 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 30% ether−pentane) afforded the amine **14t** as a white solid (75.4 mg, 72%): R_f = 0.24 (33% ether−pentane; UV). mp 145−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.9 Hz, 2H), 4.38 (br, 1H), 3.74 (s, 3H), 3.10 (m, 2H), 1.99 (m, 4H), 1.62−1.19 (m, 8H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5 (C), 152.1 (C), 142.9 (C), 115.0 (CH), 114.2 (CH), 78.9 (C), 56.0 (CH_3), 53.9 (C), 40.4 (CH_2), 38.3 (CH_2), 35.5 (CH_2), 28.6 (CH_3), 25.8 (CH_2), 21.7 (CH_2). IR (ATR-FTIR), cm^{-1}: 3371 (m), 1704 (s), 1516 (s), 1162 (s). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{20}H_{33}N_2O_3^+$, 349.2486; found, 349.2466.

Synthesis of the Amine ***14u*** *(Table 5, Entry 11).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (13.3 mg, 27.0 μmol, 0.0900 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and mestranol (**7u**, 59.5 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The vial was placed in an aluminum block at 25 °C, and the reaction mixture was stirred for 24 h. PICB (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate−pentane) to afford product **14u** as a white solid (105 mg, 81%): R_f = 0.29 (33% ethyl acetate−pentane; UV). mp 128−130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 9.0 Hz, 2H), 6.64 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.37 (m, 2H), 2.87 (m, 2H), 2.34 (m, 1H), 2.17 (m, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.90 (m, 1H), 1.78−1.63 (m, 4H), 1.59−1.47 (m, 3H), 1.41 (m, 2H), 1.32 (m, 1H), 0.92 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.4 (C), 152.7 (C), 142.4 (C), 142.3 (C), 138.0 (C), 132.6 (C), 126.3 (CH), 115.3 (CH), 114.8 (CH), 113.8 (CH), 111.4 (CH), 83.9 (C), 55.8 (CH_3), 55.2 (CH_3), 49.4 (CH), 46.9 (CH_2), 43.8 (CH), 41.9 (CH_2), 39.6 (CH), 35.3 (CH_2), 34.9 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 27.5 (CH_2), 26.3 (CH_2), 23.4 (C). 14.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 2931 (br, m), 1513 (s), 1232 (s), 1042 (m). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{28}H_{38}NO_3^+$, 436.2847; found, 436.2838.

Synthesis of the Amine ***14v*** *(Table 5, Entry 12).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (13.3 mg, 27.0 μmol, 0.0900 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and 1-(prop-2-yn-1-yl)-1*H*-indole (**7v**, 46.6 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 36 h at 25 °C. PICB (32.1 mg, 300 μL, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and *p*-anisidine (36.9 mg, 300 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ether−pentane) to afford the product **14v** as a colorless oil (61.4 mg, 73%): R_f = 0.18 (33% ether−pentane; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9, 0.9 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.20 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.11 (m, 2H), 6.76 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 8.9 Hz, 2H), 6.51 (m, 1H), 4.28 (t, J = 6.7 Hz, 2H), 3.74 (s, 3H), 3.07 (t, J = 6.7 Hz, 2H), 2.14 (p, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4 (C), 142.3 (C), 136.1 (C), 128.8 (C), 127.9 (CH), 121.7 (CH), 121.2 (CH), 119.5 (CH), 115.1 (CH), 114.4 (CH), 109.4 (CH), 101.5 (CH), 55.9 (CH_3), 44.0 (CH_2), 42.4 (CH_2), 30.2 (CH_2). IR (ATR-FTIR), cm^{-1}: 1509 (s), 1462 (m), 1231 (s), 738 (s). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{18}H_{21}N_2O^+$, 281.1649; found, 281.1665

*Synthesis of N-Decylaniline (****S9a****, Table S1, Entry 1).* In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (7.4 mg, 15 μmol, 0.050 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and 1-decyne (**7l**, 41.5 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. Aniline (**S8a**, 28.0 mg, 300 μmol, 1.00 equiv), acetic acid (19.0 μL, 330 μmol, 1.10 equiv), and PICB (32.1 mg, 300 μmol, 1.00 equiv) were added to the reaction mixture in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate−pentane) to afford the product **S9a** as a colorless oil (65.9 mg, 83%). ^{1}H NMR data for the amine **S9a** prepared in this way were in agreement with literature values.[S1]



7l 83% **S9a**

*Synthesis of N-Decyl-N-methylaniline (****S9b****, Table S1, Entry 2).* We followed the procedure for **S9a** using *N*-methylaniline (**S11c**, 35.0

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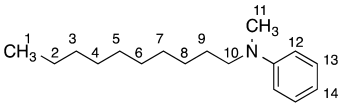
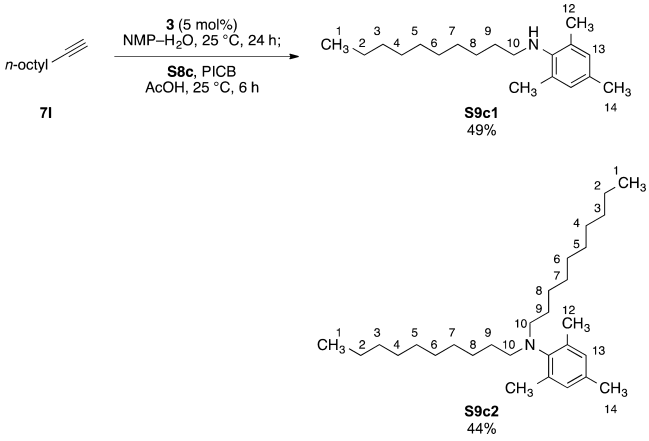


S9b

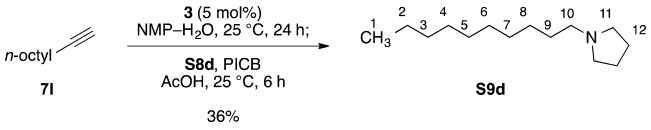
mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 30% dichloromethane−pentane) afforded the amine **S9b** as a colorless oil (50.0 mg, 67%). R_f = 0.61 (33% methylene chloride−pentane; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, J = 8.0 Hz, 2H, H_{12}), 6.71−6.63 (m, 3H, H_{13}, H_{14}), 3.27 (t, J = 7.2 Hz, 2H, H_{10}), 2.91 (s, 3H, H_{11}), 1.56 (m, 2H, H_9), 1.35−1.16 (m, 14H, H_2−H_8), 0.87 (t, J = 6.8 Hz, 3H, H_1). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5 (C), 129.3 (CH), 115.9 (CH), 112.2 (CH), 53.0 (CH_2), 38.4 (CH_3), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2922 (m), 1505 (s), 744 (s), 689 (s). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{17}H_{30}N^+$, 248.2373; found, 248.2360.

*Synthesis of the Amine **S9c1** and **S9c2** (Table S1, Entry 3).* In a nitrogen-filled drybox, an 11 mL vial was charged sequentially with a



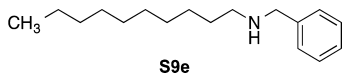
Teflon-coated stirbar, the ruthenium complex **3** (7.4 mg, 15.0 μmol, 0.0500 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL), and 1-decyne (**7l**, 41.5 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (1.0 mL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. 2,4,6-Trimethylaniline (**S8c**, 126 μL, 900 μmol, 3.00 equiv), acetic acid (56.6 μL, 990 μmol, 3.30 equiv), and PICB (32.1 mg, 300 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% methanol in dichloromethane that contains 0.6% ammonia) to afford the products **S9c1** and **S9c2** as colorless oils (**S9c1**: 40.7 mg, 49%; **S9c2**: 27.8 mg, 44%). **S9c1**: R_f = 0.14 (33% methylene chloride−pentane; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 2H, H_{13}), 2.92 (t, J = 7.3 Hz, 2H, H_{10}), 2.26 (s, 6H, H_{12}), 2.23 (s, 3H, H_{14}), 1.58 (p, J = 7.4 Hz, 2H, H_9), 1.42−1.18 (m, 14H, H_2−H_8), 0.88 (t, J = 6.7 Hz, 3H, H_1). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0 (C), 131.1 (C), 129.6 (C), 129.5 (CH), 49.1 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 19.7 (CH_2), 19.5 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 20.7 (CH_3), 18.5 (CH_3), 14.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2922 (s), 1484 (m), 1230 (m), 852 (m). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{19}H_{34}N^+$, 276.2686; found, 276.2683. **S9c2**: R_f = 0.93 (33% methylene choride−pentane; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 2H, H_{13}), 2.94 (t, J = 7.8 Hz, 4H, H_{10}), 2.25 (s, 6H, H_{12}), 2.23 (3H, H_{14}), 1.40 (p, J = 7.8 Hz, 4H, H_9), 1.32−1.15 (m, 28H, H_2−H_8), 0.875 (t, J = 7.2 Hz, 6H, H_1). ^{13}C NMR (151 MHz, $CDCl_3$) δ146.2 (C), 137.8 (C), 134.1 (C), 129.5 (CH), 54.6 (CH_2), 32.1 (CH_2), 29.9(CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.6 (CH_2), 22.8 (CH_2), 20.9 (CH_3), 19.7 (CH_3), 14.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2922 (s), 2852 (m), 1446 (m), 851 (m). HRMS-ESI(m/z): [M + H]$^+$ calcd for $C_{29}H_{54}N^+$, 416.4251; found, 416.4249.

*Synthesis of 1-Decylpyrrolidine (**S12e**, Table S1, Entry 4).* In a nitrogen-filled drybox, an 11 mL vial was charged sequentially with a



Teflon-coated stirbar, the ruthenium complex **3** (14.8 mg, 30.0 μmol, 0.0500 equiv), *N*-methyl-2-pyrrolidinone (3.0 mL), and 1-decyne (**7l**, 83.0 mg, 600 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (1.0 mL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. Pyrrolidine (**S8d**, 148 μL, 1.80 mmol, 3.00 equiv), acetic acid (113 μL, 1.98 mmol, 3.30 equiv), and PICB (64.2 mg, 600 μmol, 1.00 equiv) were then added in sequence. The reaction mixture was stirred for 6 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 0.6% ammonia in 5% methanol−methylene chloride) to afford product **S9d** as a brown oil (45.5 mg, 36%). R_f = 0.18 (0.6% ammonia in 5% methanol−methylene chloride; $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (s, br, 4H, H_{11}), 2.74 (t, J = 8.2 Hz, 2H, H_{10}), 2.00−1.94 (m, 4H, H_{12}), 1.74−1.65 (m, 2H, H_9), 1.36−1.17 (m, 14H, H_{2-8}), 0.86 (t, J = 6.9 Hz, 3H, H_1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.3 (CH_2), 54.0 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 23.5 (CH_2), 22.8 (CH_2), 14.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2921 (s), 2852 (m), 2451 (m, br), 1462 (m). HRMS-ESI(m/z): [M + H]+ calcd for $C_{14}H_{30}N^+$, 212.2373; found, 212.2350.

*Synthesis of **S9e** (Table S1, Entry 5).* We followed the procedure for **S9d** using benzylamine (**S8e**, 196 μL, 1.80 mmol, 3.00 equiv).



S9e

Purification by flash-column chromatography (eluting with 0.6% ammonia in 5% methanol−methylene chloride) afforded the amine **S9e** as a brown oil (66.0 mg, 44%). ^{1}H NMR data for the amine **S9a** prepared in this way were in agreement with literature values.[52]

*Synthesis of Phenylacetic Acid (**17j**, Table 7, Entry 1).* In a nitrogen-filled drybox, an 8 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (5.9 mg, 12 μmol, 0.020 equiv), *N*-methyl-2-pyrrolidinone (3.0 mL), and phenylacetylene (**7j**, 61.3 mg, 600 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (1.0 mL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. Bis(acetoxy)iodobenzene (399 mg, 1.20 mmol, 2.00 equiv) was added to the reaction mixture. The reaction mixture was stirred for 1 h at 25 °C. The product mixture was diluted with ethyl acetate (30 mL), and the diluted solution was transferred to

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a separatory funnel. Aqueous hydrochloric acid solution (1 M, 30 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) to afford the product **17j** as a white solid (68.9 mg, 84%). ^{1}H NMR data for the phenylacetic acid (**17j**) prepared in this way were in agreement with literature values.[53]

Synthesis of the Carboxylic Acid ***17k*** *(Table 7, Entry 2).* We followed the procedure for **17j** using 4-methoxyphenylacetylene (**7k**, 79.3 mg, 600 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 1% acetic acid in 40% ethyl acetate−pentane) afforded the carboxylic acid **17k** as a white solid (81.6 mg, 82%). ^{1}H NMR data for the carboxylic acid **17k** prepared in this way were in agreement with literature values.[54]

*Synthesis of Decanoic Acid (****17l****, Table 7, Entry 3).* In a nitrogen-filled drybox, an 8 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (14.8 mg, 30.0 μmol, 0.0500 equiv), *N*-methyl-2-pyrrolidinone (3.0 mL), and 1-decyne (**7l**, 83.0 mg, 600 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (1.0 mL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The reaction mixture was stirred for 24 h at 25 °C. Bis(acetoxy)iodobenzene (598 mg, 1.80 mmol, 3.00 equiv) was added to the reaction mixture. The reaction mixture was stirred for 1 h at 25 °C. The product mixture was diluted with ethyl acetate (30 mL), and the diluted solution was transferred to a separatory funnel. Aqueous hydrochloric acid solution (1.0 M, 30 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) to afford the product **17l** as a white solid (102 mg, 98%). ^{1}H NMR data for the decanoic acid (**17l**) prepared in this way were in agreement with literature values.[54]

Synthesis of the Carboxylic Acid ***17m*** *(Table 7, Entry 4).* We followed the procedure for **17l** using *N*-(4-pentynyl)phthalimide (**7m**, 64.0 mg, 300 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) afforded the carboxylic acid **17m** as a white solid (74.2 mg, 99%). ^{1}H NMR data for the carboxylic acid **17m** prepared in this way were in agreement with literature values.[55]

Synthesis of the Carboxylic Acid ***17n*** *(Table 7, Entry 5).* We followed the procedure for **17l** using methyl undecanoate (**7n**, 118 mg, 600 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) afforded the carboxylic acid **17n** as a white solid (130 mg, 94%): R_f = 0.64 (1% acetic acid in 50% ethyl acetate−pentane; bromocresol). mp 40−43 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.67−1.24 (m, 14H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.6 (C), 174.5 (C), 51.6 (CH_3), 34.3 (CH_2), 33.9 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.1 (CH_2), 24.8 (CH_2). IR (ATR-FTIR), cm^{-1}: 2915 (s), 2849 (s), 1704 (s), 1224 (m). HRMS-ESI(*m*/*z*): $[M + Na]^+$ calcd for $C_{12}H_{22}NaO_4^+$, 253.1410; found, 253.1411.

*Synthesis of 6-Chlorohexanoic Acid (****17o****, Table 7, Entry 6).* We followed the procedure for **17l** using 6-chloro-1-hexyne (**7o**, 70.0 mg, 600 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) afforded the carboxylic acid **17o** as a white solid (83.4 mg, 92%). ^{1}H NMR data for the carboxylic acid **17o** prepared in this way were in agreement with literature values.[56]

Synthesis of the Carboxylic Acid ***17s*** *(Table 7, Entry 7).* In a nitrogen-filled drybox, an 8 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (20.8 mg, 42.0 μmol, 0.0700 equiv), *N*-methyl-2-pyrrolidinone (3.0 mL), and 2-ethynyl-1,3,5-trimethylbenzene (**7s**, 86.5 mg, 600 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (1.0 mL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The vial was placed in an aluminum block at 25 °C, and the reaction mixture was stirred for 24 h. Bis(acetoxy)iodobenzene (797 mg, 2.40 mmol, 4.00 equiv) was added to the reaction mixture. The reaction mixture was stirred for 1 h at 25 °C. The product mixture was diluted with ethyl acetate (30 mL), and the diluted solution was transferred to a separatory funnel. Aqueous hydrochloric acid solution (1.0 M, 30 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (4 × 50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate−pentane containing 1% acetic acid) to afford product **17s** as a white solid (97.6 mg, 91%). ^{1}H NMR data for the carboxylic acid **17s** prepared in this way were in agreement with literature values.[57]

Synthesis of the Carboxylic Acid ***17t*** *(Table 7, Entry 8).* We followed the procedure for **17s** using *N*-(1-ethynylcyclohexyl)-4-methylbenzenesulfonamide (**7t**, 166.4 mg, 600 μmol, 1 equiv). Purification by flash-column chromatography (eluting with 1% acetic acid in 60% ethyl acetate−pentane) afforded the carboxylic acid **17t** as a white solid (171 mg, 91%): R_f = 0.35 (1% acetic acid in 50% ethyl acetate−pentane; UV, bromocresol). mp 162−167 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.41 (br, 1H), 2.70 (s, 2H), 2.42 (s, 3H), 1.94−1.83 (m, 2H), 1.56−1.23 (m, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5 (C), 143.4 (C), 140.0 (C), 129.7 (CH), 127.3 (CH), 57.5 (CH_2), 42.4 (C), 35.8 (CH_2), 25.3 (CH_2), 21.7 (CH_3), 21.6 (CH_2). IR (ATR-FTIR), cm^{-1}: 3365 (m), 1670 (s), 659 (s), 547 (s). HRMS-ESI(*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{22}NO_4S^+$, 312.1265; found, 312.1264.

Synthesis of the Carboxylic Acid ***17w*** *(Table 7, Entry 9).* In a nitrogen-filled drybox, an 11 mL vial was charged sequentially with a Teflon-coated stirbar, the ruthenium complex **3** (7.4 mg, 15 μmol, 0.050 equiv), *N*-methyl-2-pyrrolidinone (1.5 mL) and 2-methyl-*N*-(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)propane-2-sulfinamide (**7w**, 92.3 mg, 300 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the drybox. Water (500 μL) was then added with exclusion of oxygen (nitrogen-filled bag). The vial was sealed with a Teflon-lined cap, and the sealed vial was removed from the nitrogen-filled bag. The vial was placed in an aluminum block at 50 °C, and the reaction mixture was stirred for 24 h. (Diacetoxyiodo)benzene (398 mg, 1.20 mmol, 4.00 equiv) was added to the reaction mixture. The reaction mixture was stirred for 1 h at 25 °C. The product mixture was diluted with ethyl acetate (15 mL), and the diluted solution was transferred to a separatory funnel. Hydrochloric acid aqueous solution (1.0 M, 15 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL), and the organic layers were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (6 × 25 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid in 60% ethyl acetate−pentane) to afford product **17w** as a white solid (68.7 mg, 80%): R_f = 0.23 (1% acetic acid in 50% ethyl acetate−pentane; UV, bromocresol). mp 152−155 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47−7.20 (m, 5H), 5.65 (d, *J* = 9.5 Hz, 1H), 4.99−4.81 (m, 1H), 2.96 (q, *J* = 13.1, 10.0, 2H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.6 (C), 141.4 (C), 129.3 (CH), 128.2 (CH), 126.9 (CH), 60.5 (CH_2), 55.5 (CH), 43.0 (C), 24.4 (CH_3). IR (ATR-FTIR), cm^{-1}:

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3250 (br, m), 1698 (m), 1292 (s), 1135 (m). HRMS-ESI(m/z): $[M + H]^+$ calcd for $C_{13}H_{20}NO_4S^+$, 286.1108; found, 286.1135.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01220.

Table S1 and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (c) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121. (d) Hintermann, L. *Top. Organomet. Chem.* **2010**, *31*, 123.

(2) (a) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867. (b) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884. (c) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917. (d) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232. (e) Chevallier, F.; Breit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1599. (f) Labonne, A. l.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, *8*, 5853. (g) Boeck, F.; Kribber, T.; Xiao, L.; Hintermann, L. *J. Am. Chem. Soc.* **2011**, *133*, 8138.

(3) (a) Li, L.; Herzon, S. B. *Nat. Chem.* **2014**, *6*, 22. (b) Li, L.; Zeng, M.; Herzon, S. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7892. (c) Zeng, M.; Li, L.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 7058. For a review, see: (d) Zeng, M.; Herzon, S. B. *Aldrichim. Acta* **2014**, *47*, 55.

(4) For selected examples of metal-catalyzed functionalization of alkenes to obtain alcohols and their derivatives, see: (a) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366. (b) Takahashi, K.; Yamashita, M.; Ichihara, T.; Nakano, K.; Nozaki, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4488. (c) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (d) Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609. (e) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577. (f) Perkowski, A. J.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 10334.

(5) For reviews of metal vinylidene intermediates, see: (a) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (b) Wakatsuki, Y. *J. Organomet. Chem.* **2004**, *689*, 4092. For a review of mechanistic studies of earlier ruthenium-based anti-Markovnikov hydration catalysts that implicate vinylidene intermediates in the catalytic cycle, see: (c) Grotjahn, D. B. *Pure Appl. Chem.* **2010**, *82*, 635.

(6) Guan, H.; Iimura, M.; Magee, M. P.; Norton, J. R.; Zhu, G. *J. Am. Chem. Soc.* **2005**, *127*, 7805.

(7) For a discussion of prior efforts to effect the anti-Markovnikov hydration of propargylic alcohol derivatives, see: Hintermann, L.; Kribber, T.; Labonne, A.; Paciok, E. *Synlett* **2009**, 2412.

(8) For selected examples, see: (a) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, *8*, 447. (b) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937. (c) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (d) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197. (e) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8. For recent reviews, see: (f) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (g) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(9) Labonne, A.; Zani, L.; Hintermann, L.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 5704.

(10) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2002**, *43*, 7531.

(11) For a review, see: Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

(12) For a review of metal allenylidene complexes, see: Rigaut, S.; Touchard, D.; Dixneuf, P. H. *Coord. Chem. Rev.* **2004**, *248*, 1585.

(13) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. - Eur. J.* **2005**, *11*, 1433.

(14) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941.

(15) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518.

(16) Kalesse, M.; Quitschalle, M.; Claus, E.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem.* **1999**, 2817.

(17) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236.

(18) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.

(19) Tillack, A.; Jiao, H.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Chem. - Eur. J.* **2004**, *10*, 2409.

(20) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38.

(21) (a) Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042. (b) Arndt, M.; Salih, K. S. M.; Fromm, A.; Goossen, L. J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428.

(22) Magee, M. P.; Norton, J. R. *J. Am. Chem. Soc.* **2001**, *123*, 1778.

(23) See: Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109 and references therein.

(24) For examples of ruthenium iminoacyl complexes, see: (a) Bianchini, C.; Masi, D.; Romerosa, A.; Zanobini, F.; Peruzzini, M. *Organometallics* **1999**, *18*, 2376. (b) Sun, Y.; Chan, H.-S.; Xie, Z. *Organometallics* **2006**, *25*, 3447.

(25) For a related anti-Markovnikov hydroamination of alkenes, see: Bronner, S. M.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 101.

(26) Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, *60*, 7899.

(27) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838.

(28) For selected examples, see: (a) Gopal, H.; Gordon, A. J. *Tetrahedron Lett.* **1971**, *12*, 2941. (b) Müller, P.; Godoy, J. *Tetrahedron Lett.* **1981**, *22*, 2361. (c) Yamamoto, Y.; Suzuki, H.; Moro-oka, Y. *Tetrahedron Lett.* **1985**, *26*, 2107. (d) Dobson, J. C.; Meyer, T. J. *Inorg. Chem.* **1988**, *27*, 3283. (e) Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11380.

(29) For the rhodium-catalyzed oxidative esterification of alkynes, see: Kim, I.; Lee, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 10023.

(30) For an assisted tandem cross-metathesis−dihydroxylation sequence, see: Dornan, P. K.; Wickens, Z. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 7134.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(32) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(33) Kundig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901.

(34) Ye, L. W.; He, W. M.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 8550.

(35) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209.

(36) Liu, G. C.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(37) Kirkham, J. D.; Edeson, S. J.; Stokes, S.; Harrity, J. P. A. *Org. Lett.* **2012**, *14*, 5354.

(38) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. - Eur. J.* **2007**, *13*, 1358.

(39) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678.

(40) Barluenga, J.; Piedrafita, M.; Ballesteros, A.; Suarez-Sobrino, A. L.; Gonzalez, J. M. *Chem. - Eur. J.* **2010**, *16*, 11827.

DOI: 10.1021/acs.joc.5b01220
J. Org. Chem. 2015, 80, 8604−8618

(41) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.
(42) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447.
(43) Bording, S.; Bach, T. *Chem. Commun.* **2014**, *50*, 4901.
(44) Shan, Z. H.; Liu, J.; Xu, L. M.; Tang, Y. F.; Chen, J. H.; Yang, Z. *Org. Lett.* **2012**, *14*, 3712.
(45) Klos, A. M.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758.
(46) Kelly, A. M.; Perez-Fuertes, Y.; Fossey, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 215.
(47) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082.
(48) Jiang, N.; Ragauskas, A. J. *Org. Lett.* **2005**, *7*, 3689.
(49) Yim, J. C. H.; Bexrud, J. A.; Ayinla, R. O.; Leitch, D. C.; Schafer, L. L. *J. Org. Chem.* **2014**, *79*, 2015.
(50) Niwa, Y.; Takayama, K.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1819.
(51) Shimizu, K.; Imaiida, N.; Kon, K.; Siddiki, S. M. A. H.; Satsuma, A. *ACS Catal.* **2013**, *3*, 998.
(52) Likhar, P. R.; Arundhathi, R.; Kantam, M. L.; Prathima, P. S. *Eur. J. Org. Chem.* **2009**, 5383.
(53) Zhou, G. B.; Zhang, P. F.; Pan, Y. J. *Tetrahedron* **2005**, *61*, 5671.
(54) Qiu, J. C.; Pradhan, P. P.; Blanck, N. B.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2012**, *14*, 4034.
(55) Zav'yalov, S. I.; Dorofeeva, O.; Rumyantseva, E.; Kulikova, L.; Ezhova, G.; Kravchenko, N.; Zavozin, A. *Pharm. Chem. J.* **2002**, *36*, 440.
(56) Miura, T.; Nakashima, K.; Tada, N.; Itoh, A. *Chem. Commun.* **2011**, *47*, 1875.
(57) She, M. Y.; Xiao, D. W.; Yin, B.; Yang, Z.; Liu, P.; Li, J. L.; Shi, Z. *Tetrahedron* **2013**, *69*, 7264.

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