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A Re(V)-Catalyzed C–N Bond-Forming Route to Human Lipoxygenase Inhibitors

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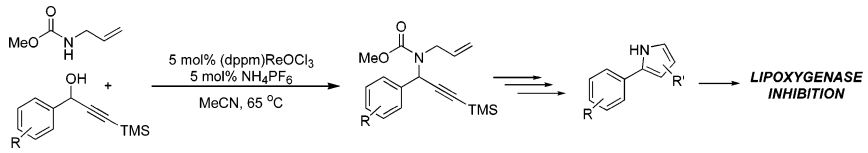
ABSTRACT



A regioselective synthesis of propargylamines by the coupling of propargyl alcohols with tosylamines and carbamates catalyzed by an air- and moisture-tolerant rhenium–oxo complex is described. The ability to couple functionalized components allows for convergent approaches to nitrogen-containing heterocyclic compounds such as the marine antibiotic pentabromopseudilin. These compounds were assayed against human lipoxygenase and found to be both potent and selective.

The biosynthesis of linear eicosanoids such as leukotrienes and lipoxins is initiated by the regio- and stereoselective hydroperoxidation of arachidonic acid.[1] This pivotal inflammation response is performed by the lipoxygense family of enzymes, which contain a catalytically active non-heme iron cofactor.[2] In addition to their native regulatory function, the lipoxygenases have been implicated in a number of human diseases such as asthma and cancer,[3] making them important targets for potential therapeutic inhibitors. Previously, we have shown that marine-derived polybrominated phenols are potent inhibitors against human lipoxygenases, which demonstrate selectivity for human reticulocyte 15-lipoxygenase-1 (15-hLO) over human platelet 12-lipoxygenase (12-hLO).[4] These initial results suggested that the degree of bromination of these inhibitors might be related to their potency; however, a modifiable chemical scaffold was required in order to perform systematic structure/function analyses. With this goal in mind, we developed a novel synthetic methodology utilizing our established oxorhenium(V)-catalyzed propargylation reaction[5] to synthesize pentabromopseudilin[6] (**1**), a marine natural product that has structural similarities to our previously discovered brominated phenol lipoxygenase inhibitors. In doing so, we hoped to extend the scope of our

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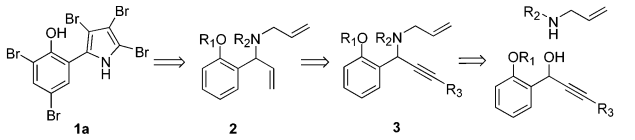
new synthetic methodology to meet the demands of the current biological study.

The need to assess the effect of halogenation on the potency of lipoxygenase inhibition precluded the synthesis of pentabromopseudilin analogues by transition metal-catalyzed biaryl coupling. In view of this, we envisioned the preparation of the required analogues by the strategy outlined in Scheme 1, in which diene **2** can be obtained from

Scheme 1

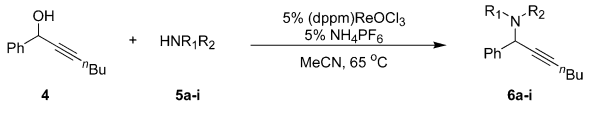


propargylic amine **3**. In turn, propargylic amines **3** could be readily prepared from simple amines and aryl propargyl alcohols[7] using our rhenium-catalyzed propargylic substitution reaction.[5] Avoiding the requirement for prior activation of either the alcohol[8] or the amine, we hoped the mild conditions for the substitution reaction would allow for the rapid synthesis of **1a**, as well as analogues with diverse substitution patterns.

Beginning our investigation of this new catalytic reaction, the addition of allylamine (**5a**) to propargylic alcohol **4** in the presence of a rhenium(V)−oxo catalyst, (dppm)$ReOCl_3$,[9] and ammonium hexafluorophosphate in acetonitrile failed to yield the desired propargylic amine (eq 2). Presumably, competitive binding of the Lewis basic amine to the rhenium center precluded the complexation of the propargylic alcohol necessary for catalytic activity. Thus, we reasoned that attenuation of the Lewis basicity of the nitrogen nucleophile would allow for a more viable catalytic process. Gratifyingly, reaction of *p*-nitroaniline (**5b**) and *p*-toluenesulfonamide (**5c**) with **4** under the catalytic reaction conditions gave the desired propargylic amine adducts in good yields and without contamination from bispropargylated products.[10] Additionally, *N*-alkyl (**5d**) and *N*-aryl (**5e**) derivatives participated equally well in the propargylic amination without the need for stoichiometric activation of either the sulfonamide or the alcohol.[11] In all cases, the propargylic amines were produced without contamination by regioisomeric allenic sulfonamides or products derived from reaction of **4** with acetonitrile.[12] Furthermore, under these conditions, the rearrangement of the propargyl alcohol to an α,β-unsaturated ketone[13] was completely suppressed.

Encouraged by these results, we considered employing other protected amines as nucleophiles in the reaction. In particular, the diverse protocols for the cleavage of carbamate protecting groups made them synthetically attractive for our purposes; however, the use of carbamates as nucleophiles typically requires the stoichiometric deprotonation of the carbamate N−H.[14] As a result, we were pleased to find that a wide range of common carbamates participated effectively in the (dppm)$ReOCl_3$-catalyzed substitution without the need for a stoichiometric base (Scheme 2).

Scheme 2



4 **5a-i** **6a-i**

a) R_1=H, R_2=allyl	(0 %)	f) R_1=EtOOC-, R_2=allyl	(83 %)
b) R_1=H, R_2=*p*-C_6H_4-NO_2	(71 %)	g) R_1=Alloc-, R_2=allyl	(78 %)
c) R_1=Ts, R_2=H	(66 %)	h) R_1=Cbz-, R_2=allyl	(92 %)
d) R_1=Ts, R_2=Me	(66 %)	i) R_1=Fmoc-, R_2=allyl	(67 %)
e) R_1=Ts, R_2=*p*-C_6H_4-OMe	(67 %)		

With these preliminary results in hand, the substrate and nucleophile scope of this reaction was investigated (Table 1). Substitution occurred with a range of propargylic alcohol substrates, including phenyl (entries 1−5) and aryl rings substituted with electron-withdrawing (entry 10) and electron-donating (entries 11−13) groups. Additionally, both sterically encumbered ortho disubstituted (entries 8 and 9) and heteroaromatic (entry 15) substrates cleanly participated in good yield. Aryl−halide bonds are unaffected by the transformation (entries 6, 7, and 10). Notably, amides are unreactive toward propargylation (entry 14), allowing for orthogonal protection of nitrogen functionality in the propargylic adduct. A variety of substituents on the alkynyl moiety are equally well tolerated. Simple methyl and primary alkyl substituents are exemplary, and although slightly increased reaction temperatures were required, the more sterically demanding phenyl (entry 4) and trimethylsilyl (entries 6, 7, and 12−14) groups also perform well. Substrates containing a terminal alkynyl unit also participate in the reaction, although in somewhat diminished yields (compare entries 8 and 9). Other potentially reactive groups, including terminal olefins (entry 5) and conjugated esters (entry 11), prove tractable.

(7) For a Ru-catalyzed amination of propargyl alcohols bearing a terminal alkyne, see: (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (b) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433.

(8) Propargyl phosphonates and esters have also been employed as substrates. Cu-catalyzed: (a) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282. Ti-catalyzed (b) Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, *42*, 1655.

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(10) Amination of benzylic alcohols catalyzed by methyltrioxorhenium-(VII) (MTO) has been described: Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 324. However, the MTO-catalyzed reaction of **1** and *N*-allyl ethyl carbamate in acetonitrile (12 h, 65 °C) resulted in rearrangement to the α,β-unsaturated ketone.

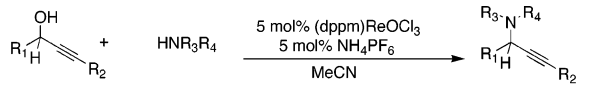
(11) For coupling of sulfonamides and propargyl alcohols using the Mitsunobu reaction, see: Bell, K. E.; Knight, D. W.; Gravestock, M. B. *Tetrahedron Lett.* **1995**, *36*, 8681.

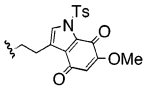
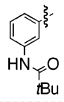
(12) Nilsson, B. M.; Hacksell, U. *J. Heterocycl. Chem.* **1989**, *26*, 269.

(13) Various metal−oxo complexes have been reported as catalysts for conversion of propargyl alcohols to enones (Meyer−Schuster rearrangement). (a) Re: Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059. (b) V: Erman, M. B.; Gulyi, S. E.; Aulchenko I. S. *Mendeleev Commun.* **1994**, 89. (c) Mo: Lorber, C. Y.; Osborn J. A. *Tetrahedron Lett.* **1996**, *37*, 853.

(14) (a) Boger, D. L.; Ishizaki, T.; Wysocki, R. J., Jr.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461. (b) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791. (c) Osipov, S. N.; Burger, K. *Tetrahedron Lett.* **2000**, *41*, 5659.

Table 1. Re(V)-Catalyzed Propargyl Substitution



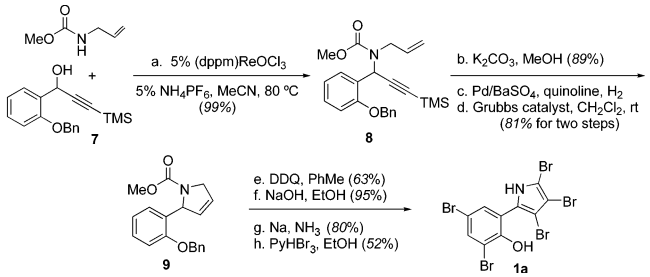
entry	R_1	R_2	R_3	R_4	temp (°C)	yield[b]
1		*n*-Bu	EtOOC-	Me	65	93
2		*n*-Bu	MeOOC-		65	69
3		*n*-Bu	Cbz-		65	82
4		Ph	Alloc-		80	52[c]
5			EtOOC-	Me	80	84
6		TMS	EtOOC-	Me	80	86
7		TMS	Cbz-		80	59
8		Me	EtOOC-	Me	65	76
9		H	EtOOC-	Me	65	55[d]
10		Me	EtOOC-	Me	65	91
11		-COOEt	EtOOC-	Me	80	80
12		TMS	Boc-		80	74
13		TMS	Cbz-	H	80	89
14		TMS	EtOOC-	Me	80	86
15		*n*-Bu	Boc-		65	85

[a] Reaction conditions: 1 M propargyl alcohol in MeCN, 3.0 equiv of amine nucleophile. [b]Isolated yield after chromatography. [c] Obtained as a mixture of diastereomers. [d] (dppm)$ReOCl_3$ (10%) and 10% NH_4PF_6 were employed.

With respect to the nucleophile, the rhenium(V)−oxo-catalyzed propargylic amination is quite general. As previously demonstrated, the choice of carbamate protecting group is largely unrestricted. Methyl and ethyl carbamates, as well as the more commonly employed Alloc, Boc, and Cbz protecting groups, all reacted effectively. Pendant olefin (entry 15) and ester (entries 3 and 7) groups and functionalized heterocycles (entry 12) are carried through the substitution event. Carbamates with branching at the α-position also participated, but the increased steric bulk leads to reduced yields of the desired substitution product (entry 4). Notably, Re-catalyzed propargylic substitution using benzyl carbamate as an ammonia equivalent also proceeded smoothly (entry 13).

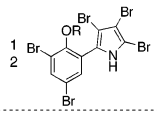
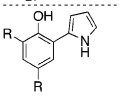
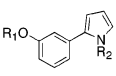
Having successfully developed the Re(V)-catalyzed C−N bond-forming reaction, we turned to the application of this methodology in the synthesis of pentabromopseudilin **1** and analogues. To begin the synthetic sequence (Scheme 3), propargylic alcohol **7**, available by nucleophilic acetylide addition to *o*-benzyloxybenzaldehyde, was catalytically aminated with *N*-allyl methyl carbamate to give adduct **8** in 99% yield. Subsequent basic desilylation and Lindlar reduction of the trimethylsilyl alkyne set the stage for ruthenium-catalyzed ring-closing metathesis[15] to afford dihydropyrrole **9**. Oxidative aromatization followed by bromination then completed the synthesis of the natural product (**1a**). The modular design of this synthetic scheme allows for facile analogue synthesis by appropriate choice of the initial substituted benzaldehyde. Compounds synthesized in this way were then advanced to biological testing.

Scheme 3. Synthesis of Pentabromopseudilin



Pentabromopseudilin (**1a**) has a structure similar to that of our previously discovered brominated phenol LO inhibitors;[4] however, its structure is more compact than our previously investigated brominated phenol ethers. Our inhibitor data of **1a** indicated that it is a potent inhibitor to 12-hLO ($IC_{50} = 13 \pm 3.6\ \mu M$), 15-hLO ($IC_{50} = 3.5 \pm 0.5\ \mu M$), and 15-sLO ($IC_{50} = 8.5 \pm 0.7\ \mu M$) (Table 2, entry 1), with a slight selectivity against 15-hLO inhibition. The mechanism of action for **1a** against 15-sLO is through reduction, as seen by the fluorescence screen,[16] presumably through the free hydroxyl on the phenyl ring. In accord with this hypothesis,

Table 2. SAR of Lipoxygenase Inhibitors

entry	compound	cLog P	IC_{50} (μM) 12-hLO	15-hLO	15-sLO	15-hLO[a] red'n
1	 (**1a**) R=H	5.9	13±3.6	3.5±0.5	8.5±0.7	No
2	(**1b**) R=Me	6.1	5.7±1.6	5.5±0.5	>1000	No
3	 (**10a**) R=Br	3.7	21±2	1.6±0.4	>100	Yes
4	(**10b**) R=Me	2.8	73±25	0.43±0.1	6.5±0.6	Yes
5	 (**11a**) R=H	1.9	52±17	3.1±0.8	2.7±0.3	Yes
6	(**11b**) R=Me	2.2	>100	>1000	>1000	n/a[b]
7	 (**12a**) R=H	2.9	>1000	>1000	>1000	No
8	(**12b**) R=Bn	5.0	7.2±1.6	3.9±1	11±1	n/a
9	 (**13a**) R_1=H; R_2=H	2.2	>1000	>1000	>1000	n/a
10	(**13b**) R_1=Me; R_2=H	2.8	>1000	>1000	>1000	n/a
11	(**13c**) R_1=Me; R_2=Et	3.8	>1000	>1000	>1000	n/a
12	(**13d**) R_1=Bn; R_2=H	4.6	10±1	7.2±0.9	>1000	n/a
13	 (**14a**) R=H; X=NH	2.8	>100	>1000	>100	n/a
14	(**14b**) R=OH; X=O	2.4	>1000	>100	>1000	n/a
15	(**14c**) R=H; X=NEt	3.8	>100	>1000	>1000	n/a
16	(**14d**) R=OMe; X=S	3.3	>1000	>1000	>1000	n/a

[a] Reduction of 15-hLO was screened with the observation of HPOD degradation. [b] n/a = samples we not screened for 15-hLO reduction due to either large IC_{50} values, which make them undetectable, or alkylation of the redox hydroxide.

methylation of the phenolic hydroxy (**1b**, entry 2) abolished the reduction of the active-site iron in 15-sLO and dramatically increased the IC_{50} ($IC_{50} > 1000\ \mu M$). In contrast, the IC_{50} of **1b** did not increase against the human enzymes 12-hLO ($IC_{50} = 5.7 \pm 1.6\ \mu M$) and 15-hLO ($IC_{50} = 5.5 \pm 0.5\ \mu M$), indicating that **1b** is not a redox inhibitor against the human enzymes and, by inference, neither is **1a**. This result was confirmed with our pseudoperoxidase assay with 15-hLO, which clearly indicates that **1a** and **1b** are not redox inhibitors of 15-hLO.

The unbrominated pyrrole **10a** showed decreased inhibition against 12-hLO ($IC_{50} = 21 \pm 2\ \mu M$) but a slightly increased potency against 15-hLO ($IC_{50} = 1.6 \pm 0.4\ \mu M$) relative to **1a**, indicating that the larger size of the brominated pyrrole ring is more important for binding to 12-hLO than 15-hLO. To probe if the bromines affect the redox potential of the phenol or the steric bulk of the inhibitor, the bromines were replaced by methyl groups (**10b**). For 12-hLO, the IC_{50} value for **10b** increased ($IC_{50} = 73 \pm 25\ \mu M$); however, the IC_{50} for 15-hLO decreased ($IC_{50} = 0.43 \pm 0.1\ \mu M$) relative to **10a** (entry 4). Considering that both **10a** and **10b** display reduction inhibition against 15-hLO, as seen by the pseudoperoxidase assay, and are of comparable size, this opposite effect on 12-hLO and 15-hLO inhibition may be due to their difference in hydrophobicity (cLogP). For **11a**, the IC_{50} for 12-hLO ($IC_{50} = 52 \pm 17\ \mu M$) increased, but for 15-hLO the IC_{50} ($IC_{50} = 3.1 \pm 0.8\ \mu M$) did not change relative to **1a** (Table 1, entry 5). These data indicate that the degree of bromination has little effect on 15-hLO inhibition; however, for 12-hLO, bromination decreases the IC_{50} approximately 5-fold. When the hydroxyl group of the unbrominated **11a** was methylated to give **11b**, the inhibition potency against both 12-hLO ($IC_{50} > 100\ \mu M$) and 15-hLO ($IC_{50} > 1000\ \mu M$) was lost. This observation implicates **11a** as a redox inhibitor, while **11b** is not, which was confirmed by the pseudoperoxidase assay for 15-hLO. This is in contrast to the methylation of pentabromopseudilin (**1a**), which did not change its potency toward 15-hLO because it is not a redox inhibitor against 15-hLO, as seen by the pseudoperoxidase assay. A possible explanation for the difference in inhibition mechanism between **1a** (nonredox) and **11a** (redox) against 15-hLO is that the larger steric bulk of the brominated **1a** could hinder the approach of the free hydroxyl moiety to the active site iron, hence prohibiting a redox mechanism but retaining its ability to bind to the active site; however, **11a** is small enough to have its hydroxyl group bind directly to the active-site iron, rendering it a redox inhibitor. Interestingly, the inhibitor potency of **11a** against 15-hLO is stronger than that against 12-hLO, indicating that positioning of **11a** in the active site of 15-hLO is more efficient for the reduction of the iron than in 12-hLO. On the other hand, **1a** presumably binds to the active site of both 12- and 15-hLO through more general hydrophobic interactions and does not require the precise positioning needed to ligate and reduce the iron.

Alkylation of the pyrrole nitrogen (**12a**) abolished all activity against 12-hLO ($IC_{50} > 1000\ \mu M$) and 15-hLO ($IC_{50} > 1000$ mM), indicating that the pyrrole nitrogen is important for inhibition activity. Interestingly, the addition of the bulky hydrophobic benzyl group in **12b** increased the inhibition potency relative to **12a** for both 12-hLO ($IC_{50} = 7.2 \pm 1.6\ \mu M$) and 15-hLO ($IC_{50} = 3.9 \pm 1\ \mu M$). A similar increase in activity was noted on benzylation of **13a** to give the isomeric benzyl ether **13d**, which showed increased activity against 12-hLO ($IC_{50} = 10 \pm 1\ \mu M$) and 15-hLO ($IC_{50} = 7.2 \pm 0.9\ \mu M$). This is an unexpected result considering that methylation at this position has little effect on potency and suggests that the large size of the benzyloxy is important, possibly as a consequence of increased steric bulk and/or hydrophobicity (cLogP). Changing the position of the hydroxyl group (from ortho to meta) drastically lowered the potency of **13a** toward 12-hLO ($IC_{50} > 1000\ \mu M$) and 15-hLO ($IC_{50} > 1000\ \mu M$) versus compound **11a**. This result substantiates our hypothesis that **11a** has a specific binding mode that allows it to bind and reduce the iron, while **13a** cannot access this binding mode due to the change in the location of the hydroxy group.

In conclusion, we have developed an air- and moisture-tolerant rhenium-catalyzed regioselective coupling of propargyl alcohols with sulfonamides and carbamates. The scope, mild reaction conditions, and experimental ease of this transformation have made it a valuable method for construction of C−N bonds in the context of bioactive nitrogen-containing heterocycles. This was demonstrated by application of this method to the construction of pentabromopseudlin and its analogues, which were examined as lipoxygenase inhibitors. With respect to the inhibition studies, we have shown that pentabromopseudilin (**1a**) is a novel and potent inhibitor against both 12- and 15-human lipoxygenase. Analogues of **1a** indicate that the degree of bromination can regulate the mode of inhibition (redox versus nonredox), with the larger brominated compounds being nonredox inhibitors. Finally, the best selectivity was observed against 15-hLO by the nonbrominated redox inhibitors **10a**, **10b**, and **11a**, which inhibited 15-hLO 13-, 170-, and 17-fold more effectively than 12-hLO, respectively.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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