OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 7992–7998

pubs.acs.org/OrgLett

Development of a Strategy for Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral γ-Hydroxyaldehyde Equivalents

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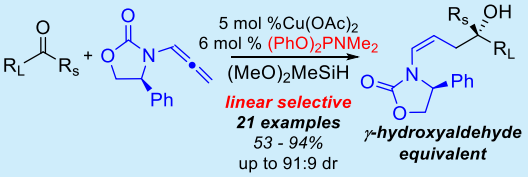
Supporting Information

ABSTRACT: We report the development of a stereoselective method for the allylation of ketones utilizing *N*-substituted allyl equivalents generated from a chiral allenamide. By choice of the appropriate ligand for the Cu-catalyst, high linear selectivity can be obtained with good diastereocontrol. This methodology allows access to chiral γ-hydroxyaldehyde equivalents that were applied in the synthesis of chiral γ-lactones and 2,5-disubstituted tetrahydrofurans.



Chiral alcohols are ubiquitous in organic molecules prepared both naturally and synthetically for a desired biological function. Therefore, development of synthetic methods to access chiral alcohols has been an intense area of research in the field of organic chemistry.[1] One of the most highly studied areas of stereoselective alcohol synthesis is in the controlled addition of an allylmetal reagent to an aldehyde or ketone electrophile.[2] Pioneering work in stereoselective allylation typically employed the generation of a stoichiometric chiral allylmetal nucleophile in a separate step to be used in the allylation reaction with an aldehyde or ketone to generate the chiral alcohol.[3] Over the years, catalytic methods to generate the reactive allylmetal *in situ* from an unreactive allyl source and metal catalyst have emerged.[4−7] In particular, reductive coupling strategies[8] that generate the reactive allylmetal from unsaturated hydrocarbons via hydrometalation are extremely powerful, atom-economical approaches for the synthesis of chiral homoallylic alcohols.[9]

Recently, an elegant catalytic method for the allylation of ketone and imine electrophiles was developed by Buchwald employing hydrocupration of carbon-substituted allenes (**2**)[10] or 1,3-dienes[11] by a Cu−H catalyst to generate the reactive allylmetal reagent *in situ* (Figure 1A). In the ketone version of this process,[10a] the *anti*-diastereomer of the branched product (*anti-b*-**3**) was formed as the major product in high diastereo- and enantioselectivity when using chiral bis(phosphine) ligands. However, the linear product *l*-**3** was not formed. Our group became interested in developing a method to generate linear products utilizing this approach, which has not been reported with ketones. While Buchwald demonstrated that both linear and branched products could be obtained when using imine electrophiles[10c] by changing the *N*-substituent on the imine, this is not possible with ketone electrophiles.

Our working mechanistic hypothesis for regio- and diasteroselectivity for this reaction is given in Figure 1B.

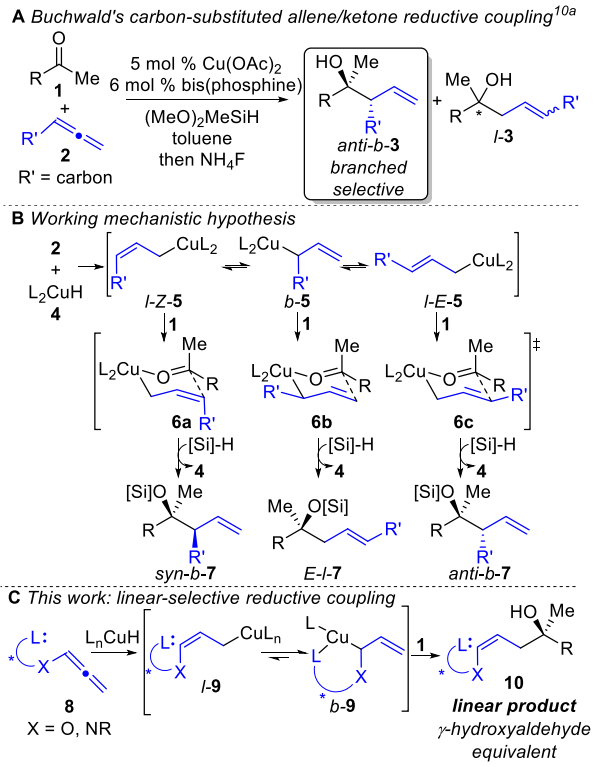


Figure 1. Cu-catalyzed reductive coupling of allenes and ketones.

Hydrometalation of allenes typically occurs *trans* to the R′-substituent of the allene due to steric reasons.[12] Therefore, initial hydrocupration of **2** would be expected to afford the *Z*-isomer of the linear (allyl)Cu species *l*-*Z*-**5**. Buchwald has

Received: August 20, 2019
Published: September 18, 2019

DOI: 10.1021/acs.orglett.9b02973
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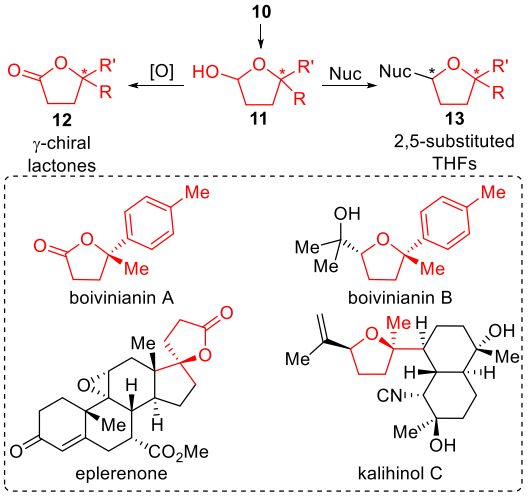
already determined that the turnover-limiting step is allylation of the ketone,[10a] so $\pi-\sigma-\pi$ equilibration of **5** would be expected. Assuming the allylation step proceeds through closed Zimmerman–Traxler[13,14] chairlike transition states (**6**), the major product obtained in Buchwald's report[10a] (*anti-b*-**3**) would be derived from *anti-b*-**7** from reaction between *l*-*E*-**5** and **1** via **6c**. The preference for this isomer can be easily rationalized by steric effects. Arguably, *l*-*E*-**5** would be the least sterically hindered of the three possible (allyl)Cu intermediates (**5**) causing it to be the dominant species in the reaction. Therefore, if this mechanistic hypothesis is correct, then to obtain the linear product (*E*-*l*-**7**), conditions would need to be designed to either stabilize the branched (ally)Cu intermediate *b*-**5** relative to *l*-**5** or make it more reactive.

Our strategy to stabilize (allyl)Cu intermediate *b*-**5** is shown in Figure 1C. Use of allene **8** containing a heteroatom tethered ligand should initially generate linear (allyl)Cu species *l*-**9** after hydrocupration. The tethered ligand could then help stabilize the branched (allyl)Cu intermediate *b*-**9** through coordination to Cu. Reaction of *b*-**9** with a ketone would then generate linear product *l*-**10** with an enol (X = O) or enamine (X = NR) group representing a masked aldehyde functionality to provide useful chiral γ-hydroxyaldehyde equivalents. Additionally, use of a chiral tethered ligand in allene **8** could enable stereocontrol of the newly formed stereocenter of **10**. Overall, we envisioned that this methodology could be a valuable entry into chiral lactone[15] or tetrahydrofuran[16] containing natural products (Scheme 1) through lactol **11** obtained by hydrolysis

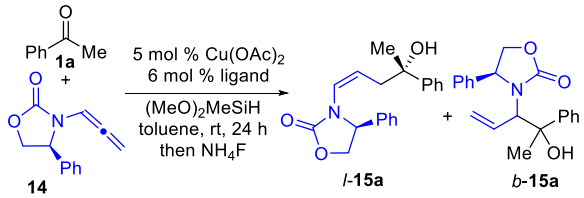
Scheme 1. Chiral Lactone and THF Containing Natural Products



of the enol or enamine functionality of **10**. Herein, we report our findings on the development of a diastereoselective copper-catalyzed reductive coupling of a chiral allenamide with ketones to access the linear isomer (**10**) of product.

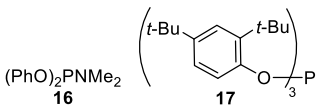
To identify an allene that fit the requirements of **8**, we initially chose to investigate allenamide **14** derived from Evans' auxiliary because it has been synthesized previously (Table 1).[17] Furthermore, we had hoped that the carbonyl group of the oxazolidinone would serve as a sufficient coordinating group for Cu.[18] Additionally, based on our design in Figure 1C, we focused on reaction conditions where Cu would have a low coordination number to facilitate potential coordination of

Table 1. Copper-Catalyzed Reductive Coupling[a]



entry	ligand	TEP[b]	θ[c]	% *l*-**15a** (dr)[d]	*l*/*b*[d]
1	PCy_3	2056	170	68 (84:16)	80:20
2	Dcpe	–	142	14 (84:16)	23:77
3	$P(t\text{-Bu})_3$	2056	182	61 (93:7)	76:24
4	$P(adam)_3$	2052	–	71 (93:7)	71:29
5	SPhos	–	–	7 (68:32)[e]	9:91
6	XPhos	–	–	5	12:88
7	*t*-BuXPhos	–	–	5	26:74
8	$P(o\text{-tol})_3$	2067	194	14 (81:19)	70:30
9	$P(NMe_2)_3$	2062	157	79 (87:13)	83:17
10	$P(OEt)_3$	2076	109	90 (83:17)	92:8
11	**16**	–	–	97 (90:10)	97:3
12	**17**	–	–	89 (92:8)	97:3
13	$P(OPh)_3$	2085	128	76 (89:11)	99:1
14	$P(C_6F_5)_3$	2091	184	12 (85:15)	99:1

[a]**1a** (0.25 mmol) and **14** (0.30 mmol) in 0.5 mL of toluene. See the Supporting Information for details. [b]Tolman electronic parameter from ref 19. [c]Ligand cone angle obtained from ref 19a. [d]Determined by ^{1}HNMR spectroscopy on the unpurified reaction mixture. [e]dr of *b*-**15a**.



the oxazolidinone carbonyl group (i.e., noncoordinating solvents, monodentate ligands).

Trialkyl monodentate phosphines favored the formation of linear product *l*-**15a** with modest *l*/*b* selectivity (entries 1, 3, and 4). Furthermore, use of dcpe, a bidentate ligand commonly employed in Cu–H catalyzed reductive coupling reactions,[10,11] also gave preferentially the branched product (entry 2). A further survey of monodentate phosphine ligands of varying electronic[19] and steric[19a] properties revealed that the linear selectivity was largely influenced by the electron-donating ability of the ligand employed with less electron-donating ligands affording higher linear selectivities (compare entries 1, 3, 4, and 8–14). There was a rough correlation between ligand cone angle and diasterocontrol with larger ligands affording higher diastereoselectivity (compare entries 1, 3, 4, 9, 10, 12, and 13). Ultimately, phosphoramidite ligand **16** afforded the highest reaction yield with excellent linear selectivity and good diastereoselectivity.

The substrate scope for the linear-selective reductive coupling of ketones and allene **14** is given in Scheme 2. In general, high linear selectivity was obtained in good to excellent reaction yield for halogenated (*l*-**15f,i**), electron-rich (*l*-**15b,c,j,k**), and electron-poor (*l*-**15e,m**) arenes. Hindered ketones bearing *ortho*-substitution on the aryl group required heating to achieve full conversion; however, this did not severely reduce the diastereoselectivity (*l*-**15c,h,i**). Additionally, diastereoselectivity and linear selectivity were reduced when the steric bias between the two R-groups of ketone **1** was reduced (*e.g.* *l*-**15d,l,n,o,p,u**). Notably, a nitrile

DOI: 10.1021/acs.orglett.9b02973
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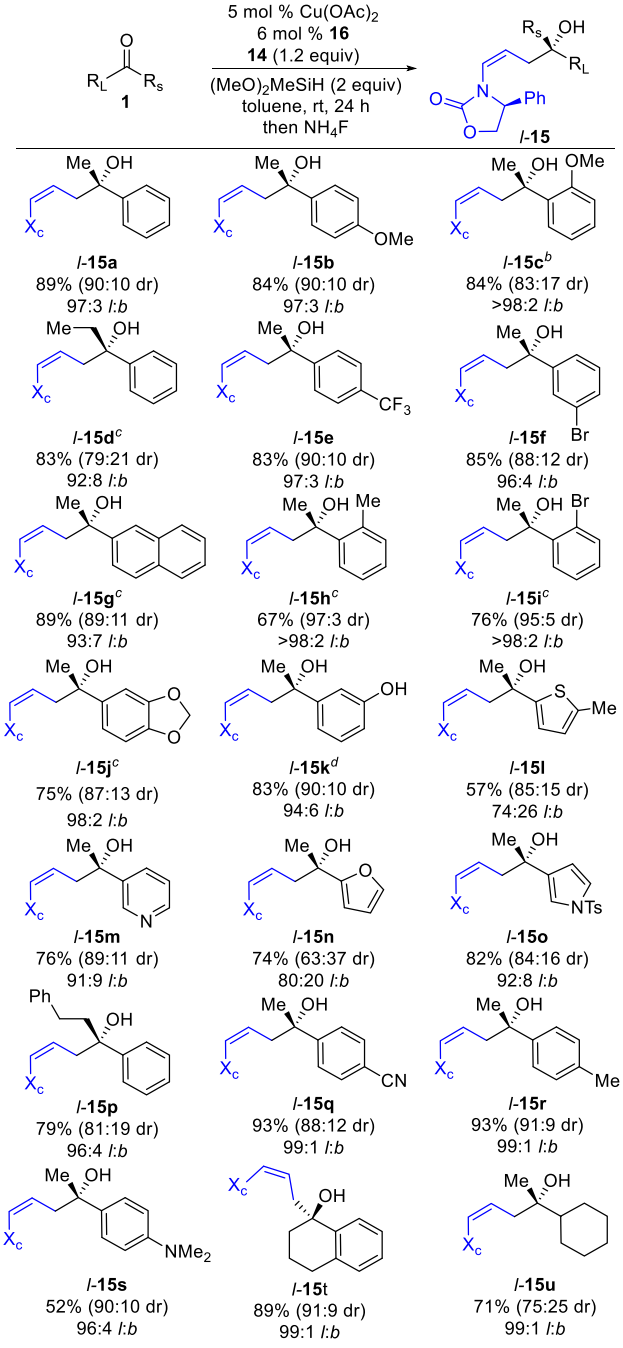
Scheme 2. Linear Selective Copper(phosphoramidite) Catalyzed Reductive Coupling[a]

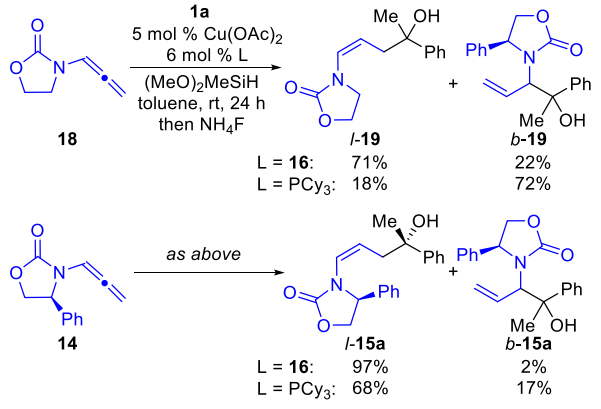


[a]Percent yield represents isolated yield of linear product as a mixture of two diastereomers on 0.5 mmol scale of **1** using 1.2 equiv of **14**; see the Supporting Information for further details. Diastereomeric ratios (dr) and linear:branched ratios (*l*:*b*) were determined by ^{1}H NMR spectroscopy on the unpurified reaction mixture. [b]Reaction performed at 60 °C. [c]Reaction performed at 40 °C. [d]4.0 equiv of $Me(MeO)_2SiH$ used.

group was not reduced under the reaction conditions (*l*-**15q**), and both amino (*l*-**15s**) and a free hydroxyl group (*l*-**15k**) was also tolerated.

In regards to factors dictating branched/linear selectivity and stereocontrol in these reactions, studies employing achiral allenamide **18** were informative (Scheme 3). Use of **18** lacking substitution on the oxazolidinone ring afforded reduced linear

Scheme 3. Effect of Oxazolidinone Structure on Regioselectivity



selectivity in the reaction when the optimized ligand **16** was used. Additionally, use of PCy_3 in the reaction employing allenamide **18** led to a turnover in the reaction selectivity and favored formation of the branched product *b*-**19**. In contrast, with chiral allenamide **14**, use of PCy_3 as a ligand afforded linear selectivity (Scheme 3 and Table 1, entry 1). Based on these observations, and the results of our ligand optimization survey (Table 1), a model to rationalize regio- and stereocontrol in these reactions could be developed (Figure 2).

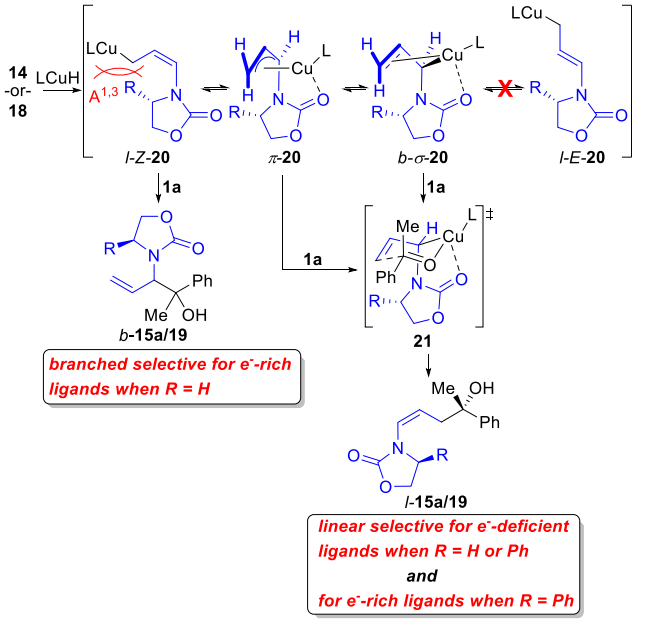


Figure 2. Stereo- and Regiochemical model.

Mechanistically, hydrocupration of allene **14** or **18** is expected to initially form the *Z*-linear (σ-allyl)Cu complex (*l*-*Z*-**20**; *vide supra*) that will be in equilibrium with the branched (σ-allyl)Cu complex (*b*-σ-**20**) through the intermediacy of the (π-allyl)Cu complex π-**20**. The π-allyl geometry and coordination of the oxazolidinone group to Cu in complex π-**20** are proposed based on structural information determined by X-ray crystallography and NMR spectroscopy for related anions of this type found in the literature.[20] Considering the turnover-limiting step in Cu-catalyzed reductive coupling of ketones and allenes is believed to be the addition of the (allyl)Cu reagent to the ketone electrophile,[10] this would allow for a pre-

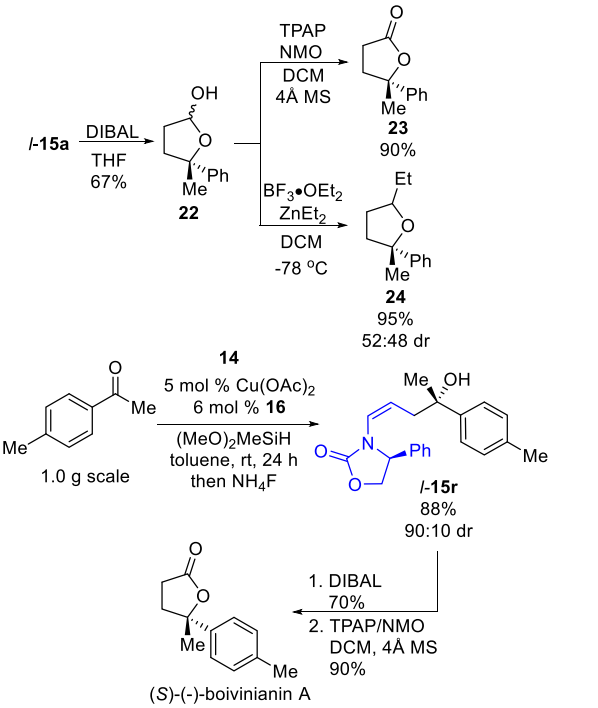
DOI: 10.1021/acs.orglett.9b02973
Org. Lett. 2019, 21, 7992−7998

equilibrium between *l*-*Z*-**20** and *b*-*σ*-**20** to be established before reaction with the ketone. Therefore, a model to rationalize regioselectivity in the reaction could be developed based on considering the stability of these two intermediates whereby a preference for *l*-*Z*-**20** would result in a branched selective process while preference for *b*-*σ*-**20** in the reaction would result in linear selectivity.[21]

Due to the *Z*-olefin geometry formed in the initial hydrocupration event, reaction regioselectivity could be explained by a competition between the strength of the oxazolidinone coordination versus the size of the $A^{1,3}$-strain present in *l*-*Z*-**20** (Figure 2). The high linear selectivity obtained as the electron-donating ability of the phosphine ligand decreases (Table 1) can be explained by an increase in the preference for complex *b*-*σ*-**20** due to the enhanced electrophilicity at Cu. Additionally, the magnitude of the $A^{1,3}$-strain in *l*-*Z*-**20** would be expected to affect the overall equilibrium between the (allyl)Cu complexes. As a result, when the poorly electron-donating ligand **16** is employed, coordination of the oxazolidinone to the electrophilic Cu atom leads to a preference for *b*-*σ*-**20** leading to linear selectivity when using either allenamide **14** or **18**. A reduction in linear selectivity with ligand **16** when using allenamide **18** in place of **14** can be rationalized by the presence of increased amounts of *l*-*Z*-**20** due to the reduction in the magnitude of the $A^{1,3}$-strain present in *l*-*Z*-**20** when R = H. In contrast, when the electron-rich ligand PCy_3 is used, the branched product (*b*-**19**) is preferred when the unsubstituted allenamide **18** was used. This may result from a shift in the equilibrium of the (allyl)Cu complexes to favor *l*-*Z*-**20** because of the reduced coordinating ability of the oxazolidinone to the more electron-rich Cu atom. When the magnitude of the $A^{1,3}$-strain present in *l*-*Z*-**20** is increased by utilizing the chiral allenamide **14** with PCy_3 as ligand, the oxazolidinone coordination is presumably enhanced by destabilizing *l*-*Z*-**20** leading to preferential linear selectivity in the reaction. Furthermore, it is important to point out that if the $A^{1,3}$-strain present in *l*-*Z*-**20** is involved in governing regiochemical control in this reaction, then the alkene moiety in *b*-*σ*-**20** likely remains coordinated to Cu.[22] If the alkene of *b*-*σ*-**20** were to disassociate from Cu, isomerization of the *Z*-alkene to the *E*-isomer *l*-*E*-**20** could occur that would remove this $A^{1,3}$-interaction that is proposed to be important. Additionally, it is possible that *b*-*σ*-**20** may not be a discrete intermediate in these reactions, and rather, *π*-**20** may be the dominant species that reacts directly with ketone **1a** to afford linear product *l*-**15a**/**19**.[22] However, this scenario is also consistent with the model described above for regiocontrol. Finally, the absolute stereochemistry and the *Z*-olefin geometry of the linear product *l*-**15a** can be rationalized by the reaction of *b*-*σ*-**20** or *π*-**20** with ketone **1a** through chair-transition state **21** with the oxazolidinone group in an axial position and complexed with Cu for selective reaction to the *Si*-face of **1a**. Transition state model **21** is supported by literature precedent[20b,c] and further supports oxazolidinone coordination in these processes.

Demonstration of the synthetic potential of the reductive coupling products is outlined in Scheme 4. Reduction of the oxazolidinone of *l*-**15a** with excess DIBAL afforded lactol **22** after hydrolysis of the resultant eneamine formed in the reduction to unmask the chiral *γ*-hydroxyaldehyde equivalent. Lactol **22** could then be converted to chiral *γ*-lactone **23** by oxidation with TPAP/NMO or converted to the 2,5-substituted tetrahydrofuran **24** in good yield albeit with poor

Scheme 4. Synthetic Applications



diastereocontrol in the Et_2Zn addition.[23] Finally, the linear selective reductive coupling reaction was performed on a 1.0 g scale to complete a three-step asymmetric synthesis of the natural product (*S*)-(−)-boivinianin A[15a−c] starting from 4′-methylacetophenone.

In conclusion, we have disclosed a strategy for the stereoselective reductive coupling of ketones and a chiral allenamide to selectively generate the linear reaction products providing useful chiral *γ*-hydroxyaldehyde equivalents. This method employs simple starting materials and a readily available catalyst system to furnish chiral products with increased complexity in an efficient manner. Further development of this reaction to enable stereocontrol by a chiral catalyst is currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02973.

Experimental procedures and characterization data for all compounds and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.9b02973
Org. Lett. 2019, 21, 7992−7998

■ ACKNOWLEDGMENTS

Startup funding from the Virginia Commonwealth University and the Bill and Melinda Gates Foundation (The Medicines for All Institute, Grant Number OPP#1176590) is gratefully acknowledged. We thank Dr. Joseph Turner (VCU) for assistance in collecting HRMS data.

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(22) For discussion purposes, intermediates π-**20** and *b*-σ-**20** were considered as discrete intermediates; however, it is possible that these are a single species. For instance, the actual intermediate formed from the isomerization of *l*-*Z*-**20** could be a distorted (π-allyl)Cu complex of type π-**20** with the Cu-atom shifted towards the C-atom of the π-allyl bearing the oxazolidinone substituent because of the directing effect. This possibility needs further investigation but would still be consistent with the model proposed for regiocontrol in this transformation.

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