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Cu-Catalyzed Enantioselective Allylic Alkylation with a γ-Butyrolactone-Derived Silyl Ketene Acetal.

Carina I. Jette,[1] Z. Jaron Tong,[2] Ryan G. Hadt,*[2] and Brian M. Stoltz*[1]

Abstract Herein, we report a Cu-catalyzed enantioselective allylic alkylation using a γ-butyrolactone-derived silyl ketene acetal. Critical to the development of this work was the identification of a novel mono-picolinamide ligand with the appropriate steric and electronic properties to afford the desired products in high yields (up to 96%) and high ee (up to 95%). Aryl, aliphatic, and unsubstituted allylic chlorides bearing a broad range of functionality are well-tolerated. Spectroscopic studies reveal that a Cu^{I} species is likely the active catalyst, and DFT calculations suggest ligand sterics play an important role in determining Cu coordination and thus catalyst geometry.

γ-Butyrolactones are important structural motifs present in numerous natural products and pharmaceutically-relevant molecules, and are also useful synthetic building blocks that serve as precursors for other highly functionalized molecules.[1] Although there are a number of reports on the α-functionalization of γ-butyrolactones to form chiral quaternary centers, only a limited number of examples have demonstrated the construction of chiral α-*tertiary* γ-butyrolactones. Some previously disclosed strategies include chiral auxiliary-directed alkylation and subsequent cyclization[1b], Claisen-type rearrangements[1c] and catalytic hydrogenation approaches.[1d] However, reports on the construction of these molecules via enantioselective α-functionalization remain limited, as the potential for racemization of the product necessitates the development of exceptionally mild reaction conditions.[2]

Since the seminal report by Tsuji,[3] transition-metal catalyzed allylic alkylation of enolate-derived nucleophiles continues to be a powerful approach for α-functionalization of carbonyl-containing compounds, as the alkene may be easily converted to a diverse array of functional groups. Nonetheless, the use of γ-butyrolactones in this transformation remains underdeveloped.[4]

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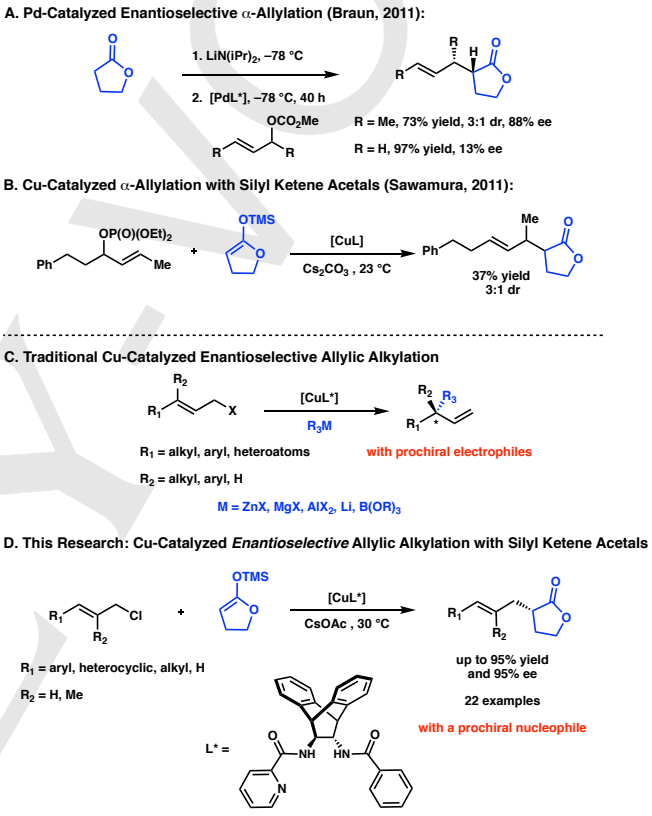

Figure 1. Transition-metal catalyzed α-allylation of γ-butyrolactones.

More specifically, there is only one example on the use of this transformation to produce enantioenriched α-tertiaryl lactones.[4c] Although the desired product is obtained in moderate diastereoselectivity and good ee when an electrophile possessing terminal substitution is used, the ee is extremely low when simple allyl carbonate is employed (Figure 1A). As part of our ongoing interest in exploring first row transition metals in enantioselective catalysis,[5] we became interested in a system reported by Sawamura, wherein a Cu catalyst was used to obtain the desired α-allyl γ-butyrolactone in a racemic fashion by reaction of silyl ketene acetals with allylic phosphates (Figure 1B).[6] It should be noted that Cu as a catalyst in allylic substitutions with hard, organometallic nucleophiles (pka >40) has been extensively studied, and the desired branched products can be accessed in high yields and enantioselectivities (Figure 1C).[7] However, the use of Cu with softer, enolate derived nucleophiles (pka < 30), remains underdeveloped.[8,9]

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One challenge associated with the development of the enantioselective variant of this transformation is that it involves a prochiral *nucleophile*, which, to our knowledge, is unprecedented in Cu-allylic alkylations. For this reason, we believed that we would not be able to rely on chiral ligand scaffolds previously used in this type of transformation. Herein, we report a Cu-catalyzed asymmetric allylic alkylation with a γ-butyrolactone-derived enolate.

Upon examination of more than 20 commercially available ligands, we found cyclohexyl bis-picolinamide ligand **L1** (Table 1, entry 1) was the only ligand to impart any degree of stereocontrol.[10] Although encouraged by these results, we soon found that the reaction outcome was highly variable, and after careful examination of all the reaction parameters, we concluded that the source of variability was the ligand itself. As a consequence of the large number of coordinating atoms present and its high flexibility, we believed **L1** could bind to Cu in a variety of conformations. As a result, small changes in the reaction set-up could alter the distribution of different Cu complexes in solution. We found that by employing mono-picolinamide **L2** as the ligand, $CuCl_2$ as the Cu source, and by deprotonation of both amide hydrogens on the ligand with *n*-BuLi, we were able to consistently obtain our product in moderate yields and ee (entry 2).

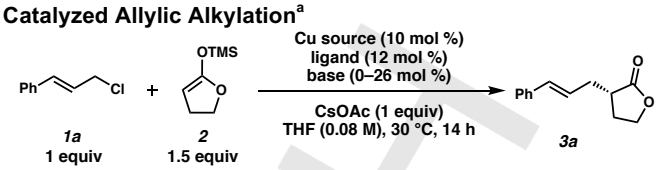
To determine whether the benzamide moiety was critical for reactivity and selectivity, we tested ligands bearing a mono-imine (**L3**), an ester moiety (**L4**) and a sulfonamide (**L5**). The anionic benzamide appears to be especially important for stereocontrol, as removing this moiety led to a drastic decrease in ee (**L3** and **L4**, entries 3 and 4). In comparison, anionic sulfonamide-containing **L5** performed most similarly to **L2** (entry 5). Interestingly, we found the ee was insensitive to the identity of the organic substituent on the amide; although the use of naphthylamide **L6** and pivalamide **L7** resulted in very different yields, the ee's were identical (entries 6 and 7).

After synthesizing and testing a number of chiral mono-picolinamide ligands, we found that a bulkier backbone (**L8**, entry 8) was crucial for consistently high levels of reactivity and selectivity. We also noted that altering the electronics at the position *para*- to the nitrogen (**L9** and **L10**, entries 9 and 10) or increasing the steric bulk of the pyridine moiety (**L11**, entry 11) led to no improvement in yield or ee.

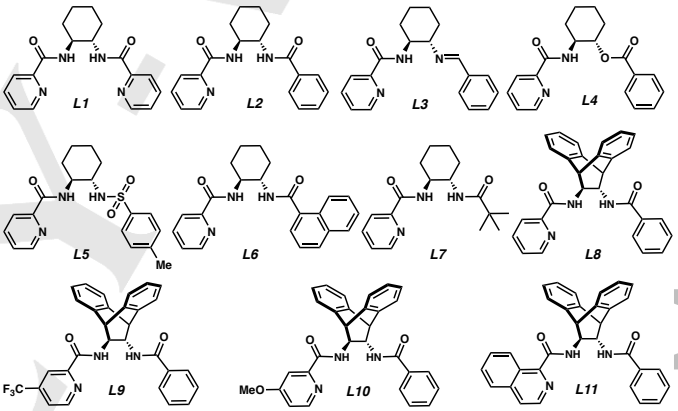
Upon more extensive optimization we found that lowering the reaction concentration from [0.08 M] to [0.042 M] led to a slight increase in ee, and with 5 mol % Cu, the reaction was complete in 6 h (entry 12).[11] Furthermore, we noted that the counterion on the catalytic base did have an effect on the overall outcome of the reaction: when NaHMDS (entry 13) or KHMDS (entry 14) is used instead of LiHMDS, the ee is slightly reduced but the reaction is complete in only 3 hours.

With optimized conditions in hand, we examined the scope of the electrophile (Table 2). We were pleased to find 2-naphthyl **3c** and *ortho*- methylphenyl (**3d**) substituents were well tolerated. *Meta*-phenyl substituted electrophiles (**3b**, **3e**) also fared well, and even a sensitive triflate (**3f**) and a bulky 3,5-dimethoxy phenyl

Table 1. Evaluation of Ligands for Enantioselective Cu-Catalyzed Allylic Alkylation[a]



entry	Cu source	base	ligand	yield (%)[b]	ee (%)[c]
1	$[Cu(MeCN)_4]PF_6$	none	***L1***	74	22
2	$CuCl_2$	*n*-BuLi (24 mol %)	***L2***	44	62
3	$CuCl_2$	*n*-BuLi (12 mol %)	***L3***	60	11
4	$CuCl_2$	*n*-BuLi (12 mol %)	***L4***	64	14
5	$CuCl_2$	*n*-BuLi (24 mol %)	***L5***	44	40
6	$CuCl_2$	*n*-BuLi (24 mol %)	***L6***	54	62
7	$CuCl_2$	*n*-BuLi (24 mol %)	***L7***	33	62
8	$CuCl_2$	LiHMDS (26 mol %)	***L8***	90	92
9	$CuCl_2$	LiHMDS (26 mol %)	***L9***	73	91
10	$CuCl_2$	LiHMDS (26 mol %)	***L10***	83	89
11	$CuCl_2$	LiHMDS (26 mol %)	***L11***	80	87
12[d]	**$CuCl_2$**	**LiHMDS (13 mol %)**	***L8***	**90**	**94**
13[d,e]	$CuCl_2$	NaHMDS (13 mol %)	***L8***	94	87
14[d,e]	$CuCl_2$	KHMDS (13 mol %)	***L8***	95	85



(a) 0.1 mmol scale. (b) Determined by ^{1}HNMR analysis of the crude reaction mixture using 1,3,5–trimethoxybenzene as a standard. (c) Determined by chiral SFC analysis. (d) 5 mol% $CuCl_2$, 6 mol% ligand, 0.042 M, 6 h. (e) 3 h reaction time.

group (**3g**) led to products in high yield and ee. Electrophiles possessing substituents at the *para*-phenyl position such as halogens (**3i**, **3j**, **3k**) a trifluoromethyl (**3l**) and a nitrile (**3m**) were were also well-tolerated. Even heterocyclic compounds (**3n** and **3o**), a diene substrate (**3p**), an aliphatic allylic chloride (**3q**) and unsubstituted allyl chloride (**3r**) led to product formation in good yields and ee's.

Although trisubstituted olefin **1s** (Scheme 1) led to the desired product **3s** in good selectivity and yield, the product formed from α-,α-substituted olefin **1t** was obtained in significantly lower yield and ee. Intrigued by this result, we exposed *Z*-olefin substrate **1u** to our reaction conditions. Interestingly, we obtained the corresponding *Z*-olefin product **3u** in good yield, but in only moderate ee. Furthermore, we also noted that even when a mixture of linear and branched electrophiles is used, only the linear product is obtained (**3v**). Taking these results into account, and also considering that other electrophiles such as benzyl or phenethyl chloride result in no product formation, we believe the reaction is proceeding through a $Cu^{III}[\sigma+\pi]$ allyl species (Scheme 2, **D**).[12]

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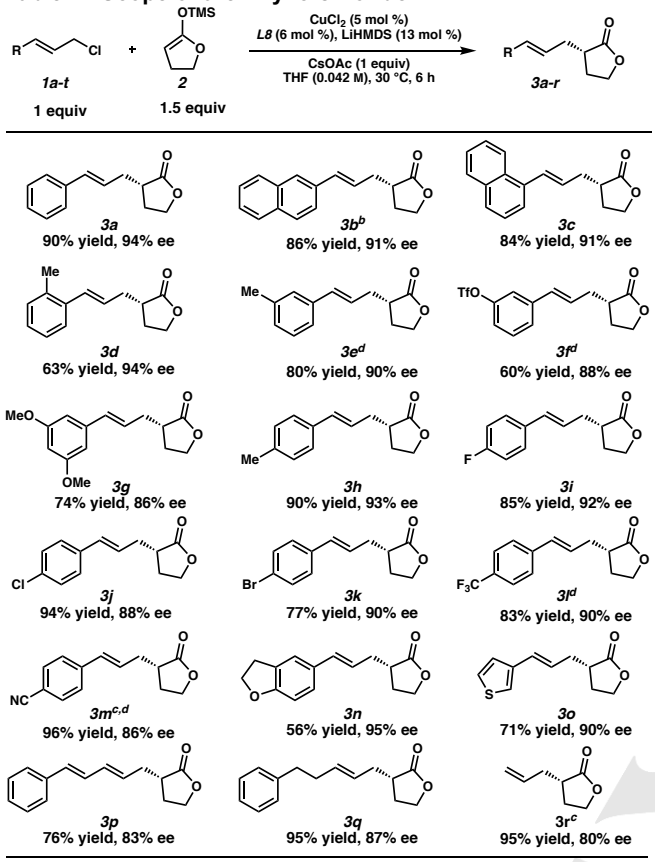
Table 2. Scope of the Allylic Chloride[a]

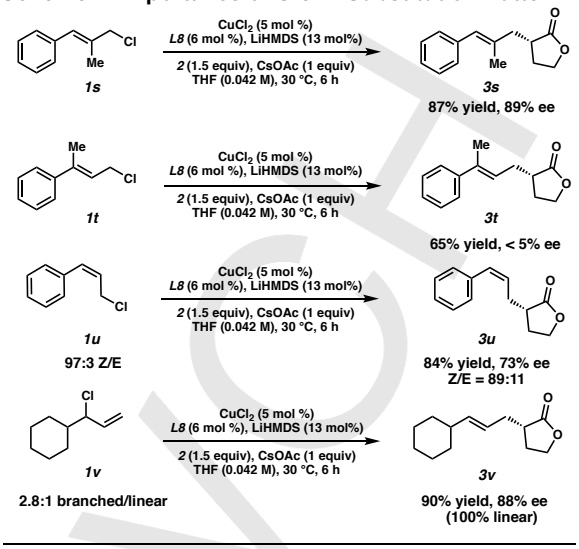


(a) Isolated yields on 0.2 mmol scale. SFC analysis was used to determine ee. (b) Absolute stereochemistry was determined by X-ray diffraction. (c) With 10 mol % $CuCl_2$, 12 mol % ***L8***, and 26 mol % LiHMDS. (d) synthesized from a mixture of linear and branched allylic chlorides (see the SI for more details).

Given the novelty of the Cu/**L8** complex, we chose to examine it using continuous wave (CW) X-band electron paramagnetic resonance (EPR), UV-vis spectroscopies, and density functional theory (DFT) calculations. Although the crystal structure of a planar Cu^{II} complex with a tetradentate, deprotonated **L1** has been reported,[13] it was unclear how exclusion of one of the pyridine moieties, and the presence of a large, bulky backbone would affect the binding mode of the ligand. For this reason, we aimed to determine whether our best performing ligand **L8** coordinates through the two amide nitrogens, or if it adopts an alternative binding mode through the benzamide oxygen, similarly to the previously disclosed Mo/**L2** complex.[14]

Preparing the pre-catalyst in THF afforded a green solution with low intensity d-d transitions ranging from 560 to 1400 nm (Figure 2 and S4). Spin quantification of the 77 K X-band EPR spectra revealed a monomeric Cu^{II} center was the major species at the reaction concentration.[15] Negative ion mode ESI-MS generated product ions and isotope patterns consistent with the ionization of the fully deprotonated $[\mathbf{L8{\bullet}CuCl_2}]^{2-}$ species, indicating that the Cl- counter-ions may be playing a role in the generation of a consistent complex.

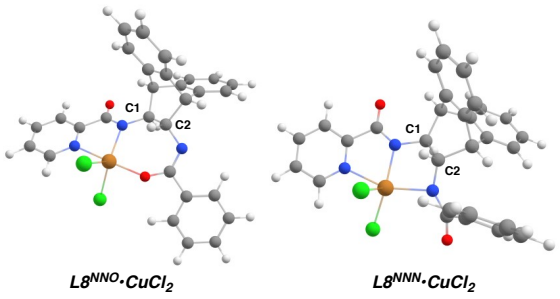
Scheme 1. Importance of Olefin Substitution Pattern[a]



(a) Isolated yields on 0.2 mmol scale. SFC analysis was used to determine ee.

DFT calculations indicate **L8** preferentially binds to Cu in a tridentate fashion, via $N_{pyridine}$, $N_{picolinamide}$, and $O_{benzamide}$ atoms ($\mathbf{L8^{NNO}{\bullet}CuCl_2}$, Table 3, entry 1). Regardless of the level of theory employed, the alternative tridentate binding mode via the benzamide nitrogen ($\mathbf{L8^{NNN}{\bullet}CuCl_2}$) is disfavored by 14-23 kcal/mol (entry 2 and Table S2). This large energy difference renders the thermal interconversion between the two binding modes unlikely; for this reason, we postulate only one conformer of the pre-catalyst accounts for the observed asymmetric catalytic activity.

Table 3. DFT Calculations on L8 and L8•$CuCl_2$[a]



entry	ligand binding mode	$E_{gas\ phase}$ (kcal/mol)	$E_{solvent\ corrected}$ (kcal/mol)[c]	τ_4' C1	τ_4' C2
with $CuCl_2$					
1	$L8^{NNO}{\cdot}CuCl_2$	0	0	0.93	0.95
2	$L8^{NNN}{\cdot}CuCl_2$	22.5	19.5	0.86	0.85
without $CuCl_2$[b]					
3	relaxed $L8^{2-}$	0	0	0.96	0.97
4	$L8^{NNO}$	18.7	13.6	0.93	0.95
5	$L8^{NNN}$	39.5	30.0	0.86	0.85

(a) Obtained using B3LYP density functional with 38% Hartree-Fock exchange. (b) Ligand coordination geometry was obtained by removing $CuCl_2$ from the optimized geometry of the corresponding complex.

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To further probe the origin for this binding preference, we performed single-point calculations on **L8** in the absence of $CuCl_2$ (entries 3-5). Interestingly, we found the energy gap between the two conformations **L8**^{NNO} and **L8**^{NNN} is still retained (entries 4 and 5), implying ligand sterics affect the binding preference and tune the metal coordination geometry. As demonstrated by the geometry index τ_4',[16] the two sp^3 ring carbons **C1** and **C2** exhibit a stronger deviation from the ideal tetrahedral geometry (τ_4' = 1) in **L8**^{NNN} relative to **L8**^{NNO}.[17] Thus, in addition to providing steric bulk to assist in stereocontrol, the rigid backbone of **L8** likely plays an important role in enforcing NNO binding.

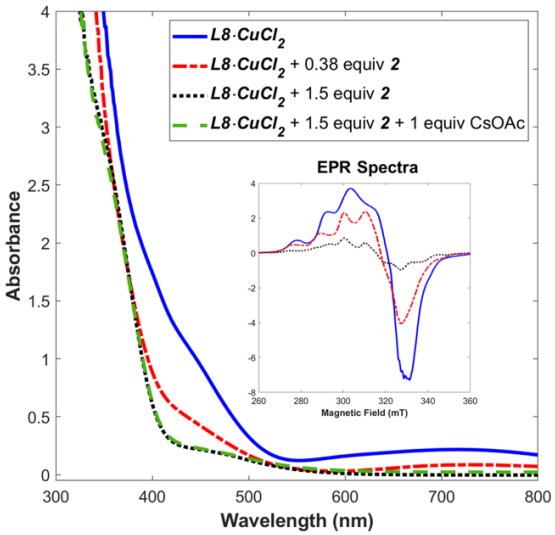
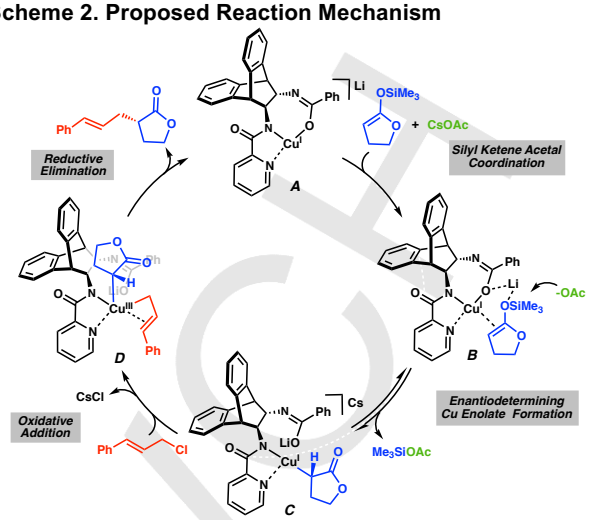


Figure 2. Room temperature UV-vis and 77 K X-band EPR (inset) spectroscopic monitoring of the reaction of 5 mol% of **L8•CuCl$_2$** with silyl ketene acetal **2**.

The characteristic d-d transitions and 77 K X-band EPR signal of the starting **L8•CuCl$_2$** complex disappear at the start of the reaction, signifying the Cu^{II} precatalyst is reduced to a Cu^{I} complex (Figure 2).[18] We found reduction occurs even in the absence of CsOAc, indicating the silyl ketene acetal **2** is the reductant.[19] Consequently, we propose the reaction follows a Cu^{I}-Cu^{III} catalytic cycle as shown in Scheme 2.[20]

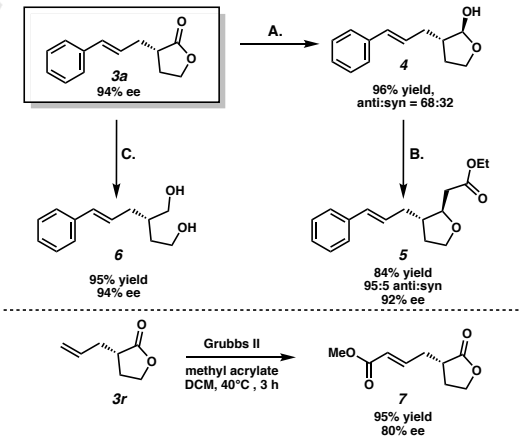
We believe the catalytic cycle commences with coordination of the electron-rich olefin of the silyl ketene acetal to Cu^{I} bis-amidate complex **A**, forming **B**. The Si-O bond is then cleaved via outer sphere attack by the acetate anion[2d] to afford the desired C-bound Cu enolate **C**.[21] We envision this could be the enantiodetermining step, during which the lithium counter-ion may assist through electrostatic interactions, preventing rotation of the silyl ketene acetal. Dissociation of the benzamide then allows for the coordination and subsequent oxidative addition of the allyl chloride, generating $Cu^{III}[\sigma+\pi]$ species **D**.[12,22] The sterically encumbered Cu^{III} species can then undergo reductive elimination to generate the desired α-allyl γ-butyrolactone and the starting Cu^{I} species **A**.

Scheme 2. Proposed Reaction Mechanism



In order to demonstrate the synthetic utility of these products, we subjected α-allyl γ-butyrolactone **3a** and **3r** to a number of transformations (Scheme 3).[23] Lactone **3a** was reduced to the corresponding lactol **4** using DIBAL-H. Lactol **4** was then converted to the unsaturated ester, which spontaneously cyclized to the corresponding tetrahydrofuran **5** in high yield and high diastereoselectivity. Lactone **3a** was also converted to the corresponding chiral diol **6** in good yields using lithium aluminum hydride. We also found **3r** could be swiftly converted to the corresponding methyl acrylate species via cross metathesis.

Scheme 3. Derivatization of Allyl γ-Butyrolactone Products



A. DIBAL-H, CH_2Cl_2, –78 °C, 30 min. (b). NaH, triethylphosphonoacetate, THF, 0 °C to 23 °C, 3 h. C. $LiAlH_4$, Et_2O, reflux, 3 h.

In conclusion, we have developed a Cu-catalyzed enantioselective allylic alkylation with a non-stabilized enolate-derived nucleophile. Critical to the development of this reaction was the identification of a novel mono-picolinamide ligand that led to product formation in high yields (up to 96%) and ee (up to 95%). A number of electrophiles with a broad range of functionality were well-tolerated in this reaction, including aryl, heteroaryl, and aliphatic allylic chlorides. DFT calculations suggest ligand sterics

play an important role in determining metal coordination geometry, leading to tri-dentate NNO Cu coordination by the ligand. Preliminary mechanistic investigations indicate that a Cu^{I} species is likely the active catalyst, and that the reaction may proceed through a $Cu^{III}[\sigma+\pi]$ intermediate. Future work will focus on gaining a deeper understanding of the reaction mechanism and expanding the scope of this reaction to include other enolate derived nucleophiles.[24]

Acknowledgements

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Keywords: Copper • Allylic Alkylation • Enolate Nucleophiles• γ-butyrolactones• Asymmetric Catalysis

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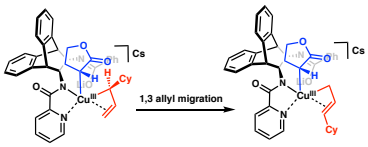
15. See S51 for more information.
16. Okuniewski, A.; Rosiak, D.; Chojnacki, J.; Becker, B. *Polyhedron*. **2015**, *90*, 47–57.
17. Although the energy gap between the two binding modes of **L2** was smaller than that of **L8,** the energy difference was still too large for thermal interconversion (Table S3).
18. We also observed a diamagnetic species by ^{1}HNMR (S234)
19. (a) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912–2914. (b) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074–16077. (c) Rathke, M.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605–4606. (d) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5724–5728. (e) Kosower, E. M.; Cole, W. J.; Wu, G. –S, Cardy, D. E.; Meisters, G. *J. Org. Chem.* **1963**, *28*, 630–633. (f) Kosower, E. M.; Wu, G. –S. *J. Org. Chem.* **1963**, *28*, 633–638.
20. The NNO binding preference was retained in a number of Cu^{II} and Cu^{I} intermediates (Table S4).
21. IR data of our Cu^{I} catalyst indicates that the benzamide dissociates upon exposure to **2**. DFT data indicates that a C-bound Cu^{I} enolate is lower in energy than the O-bound enolate (S50).
22. We believe that oxidative addition to **1v** generates a sterically congested $Cu^{III}[\sigma+\pi]$ allyl species which undergoes a 1,3 allyl migration:[12a]



23. For other potential applications of chiral α-allyl γ-butyrolactones, see S76.
24. For other nucleophiles tested, see S23.

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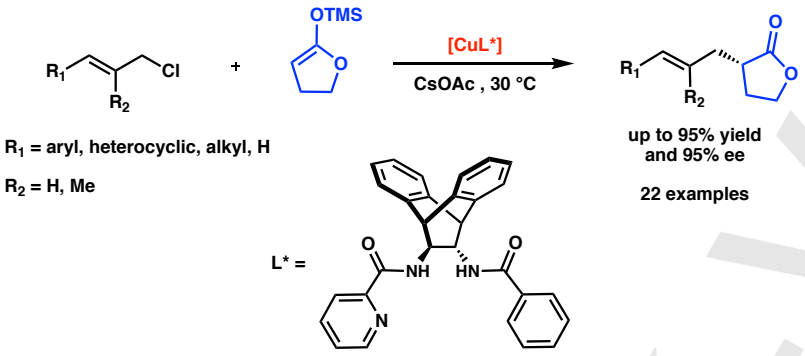

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Cu-Catalyzed Enantioselective Allylic Alkylation with a γ-Butyrolactone-Derived Silyl Ketene Acetal.

We report a Cu-catalyzed enantioselective allylic alkylation using a γ-butyrolactone-derived silyl ketene acetal as a nucleophile. Critical to the development of this work was the identification of a novel mono-picolinamide ligand with the appropriate steric and electronic properties to afford the desired alkylation products in high yields (up to 96%) and high levels of enantiomeric excess (up to 95%). DFT calculations suggest ligand sterics play an important role in determining Cu coordination and thus catalyst geometry.

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