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Enantioselective Synthesis of Highly Substituted Furans by a Copper(II)-Catalyzed Cycloisomerization−Indole Addition Reaction

Vivek Rauniyar, Z. Jane Wang, Heather E. Burks, and F. Dean Toste*

Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: A catalytic enantioselective reaction based on a copper(II) catalyst strictly containing chiral anionic ligands is described. In the present work, copper(II)−phosphate catalyst promotes the intramolecular heterocyclization of 2-(1-alkynyl)-2-alkene-1-ones and facilitates high levels of enantioselectivity in the subsequent nucleophile attack. Mechanistic studies suggest that formation of a copper(II)−indole species is important for catalysis.

Enantioselective cycloisomerization reactions have emerged as powerful methods for the asymmetric synthesis of a variety of carbo- and heterocyclic structures.[1] These reactions are most commonly catalyzed by electrophilic late transition metal complexes with chiral Lewis bases as ancilliary ligands that can decrease the electrophilicity of the metal salt; as a result, generation of a cationic variant of the ligated complex as the active catalyst is often required. While this catalyst platform has been successfully applied to rhodium,[2] iridium,[3] palladium,[4] platinum,[5] and gold[6] catalyzed enantioselective cycloisomerization reactions, its use in transformations promoted by silver and copper is rare.[7] Alternatively, unligated transition metal salts are also effective catalysts for reactions triggered by the π-activation; however, enantioselective cycloisomerization reactions employing complexes lacking chiral L-type ligands remain scarce.[8] Having realized the potential of chiral phosphates as counterions in the gold(I)-catalyzed enantioselective transformations,[9] we envisioned the utility of this motif in the form of an anionic X-type ligand for electrophilic transition metal catalysis.[10]

For this study, we chose to explore the chiral binaphthol-derived metal phosphates as potential catalysts for the asymmetric addition of nucleophiles to the positively charged putative intermediate generated from metal-catalyzed cycloisomerization of 2-(1-alkynyl)-2-alkene-1-ones (Scheme 1).[11,12] Based on the importance of the indole scaffold in medicinal chemistry, we began by examining the reaction of 2-(1-alkynyl)-2-alkene-1-one (**1**) and indole (**2**) with Ag(I)−binaphthol phosphate catalysts.[10a,b] When **1** and **2** (1.05 equiv) were treated with 5 mol % Ag(**4a**) or Ag(**4b**), we observed a quantitative conversion to **3a** in promising levels of enantioselectivity (Table 1, entry 1−2). We examined a panel of solvents for the reaction and found that fluorobenzene enhanced the enantioselectivity of the reaction without diminishing the product yield. However, when we further examined the reaction with a variety of Ag(I)-binaphthol phosphates (see Supporting Information for the complete list) at various temperatures, we were unable to optimize the reaction to beyond 74% ee.

Scheme 1. Transition Metal Catalyzed Heterocyclization

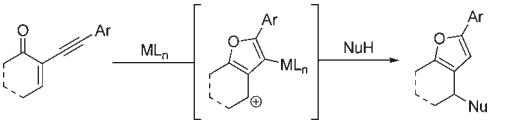
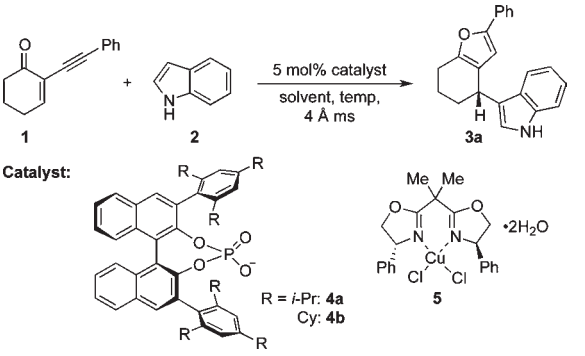


Table 1. Reaction Development[a]



Entry	Catalyst	Solvent	Temp	%Conv[b]	%ee[c]
1	Ag(I)-**4a**	toluene	rt	quant.	72
2	Ag(I)-**4b**	toluene	rt	quant.	72
3	Ag(I)-**4a**	C_6H_5F	rt	quant.	74
4	Cu(I)-**4a**	C_6H_5F	rt	quant.	80
5[d]	Cu(I)-**4a**	C_6H_5F	−15 °C	quant.	80
6	Cu(II)(**4a**)$_2$	C_6H_5F	rt	quant.	80
7[d]	Cu(II)(**4a**)$_2$	C_6H_5F	−15 °C	quant.	91
8	**5**	C_6H_5F	rt	0%	n.d.

[a] Conditions: 1.0 equiv of **1**, 1.05 equiv of **2**, 5 mol % MX or MX$_2$, 0.2 M, rt, 16 h. [b] Determined from crude reaction mixture. [c] Determined by HPLC analysis. [d] Time = 50 h.

At this point, we hypothesized that changing the metal on the catalyst may provide us with another avenue for exploration and we began to examine the reaction with copper(I) and copper(II) based complexes.[10d,e] The copper(II) salt was prepared via halide abstraction from $CuCl_2$•$2H_2O$ with 2.0 equiv of the corresponding silver phosphate (**4**) and isolated as an air and moisture stable

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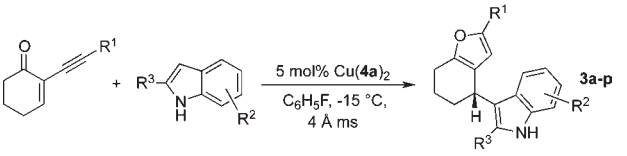
Table 2. Substrate Scope[a]



Entry	R^1	R^2	R^3	Product	% yield[b]	%ee[c]
1	Ph	H	H	**3a**	92	91
2	4-MeO-C_6H_4	H	H	**3b**	82	92
3	4-Me-C_6H_4	H	H	**3c**	85	90
4	4-F-C_6H_4	H	H	**3d**	76	88
5	4-*t*-Bu-C_6H_4	H	H	**3e**	85	90
6	3-Me-C_6H_4	H	H	**3f**	75	90
7	Cyclopentyl	H	H	**3g**	80	87
8	Bn	H	H	**3h**	84	73
9	Cyclohexyl	H	H	**3i**	85	94
10	Ph	5-Br	H	**3j**	90	93
11	Ph	6-Br	H	**3k**	94	90
12	Ph	5-MeO	H	**3l**	74	81
13	Ph	6-Me	H	**3m**	76	85
14	Ph	5-Cl	H	**3n**	81	90
15	Ph	5-F	H	**3o**	73	90
16[d]	Ph	H	Me	**3p**	16	85

[a] Conditions: 5 mol % $Cu(\mathbf{4a})_2$ added to a solution of 1.0 equiv of **1** (0.2 M) and 1.05 equiv of **2**, 50 h. [b] Isolated after chromatography. [c] Determined by HPLC analysis. [d] Conducted at 5 °C.

green solid.[13] Gratifyingly, both Cu(I)(**4a**) and $Cu(II)(\mathbf{4a})_2$ provided the desired product in high yield and enantioselectivity. While lowering the temperature had no effect on the Cu(I)-catalyzed reaction, we obtained **3a**[14] in 91% ee and quantitative conversion using the $Cu(II)(\mathbf{4a})_2$ catalyst. In contrast, use of Cu(II)-catalyst **5**, which contains a neutral Lewis basic box-ligand, failed to deliver the desired product (entry 8) in an appreciable conversion. This observation is consistent with the decreased electrophilicity of ligated copper species and demonstrates the potential advantage of X-type chiral ligands.

With the optimal catalyst and reaction conditions in hand, we explored the steric and electronic modifications on the substrate and the nucleophile. Both aromatic and aliphatic alkynes were suitable substrates for the reaction and could be readily cyclized to provide the desired furans in high yield and enantioselectivities (Table 2, entries 1−9). Similarly, electronic variations in the aryl ring of the indole scaffold were also tolerated, as both electron donating and withdrawing substituents gave the desired product in high yields and excellent enantioselectivities (entries 10−15). However, 2-methyl indole proved to be a difficult substrate for the reaction under the standard conditions as only 16% conversion to the desired product was observed after 48 h at 5 °C.

To explore the mechanism of the Ag(I) and Cu(II) catalyzed reaction, we monitored the reaction at room temperature by ^{1}H NMR. When a solution of Ag(**4a**) (2.5 mol %) was added to a solution of **1** and **2** in toluene, the reaction begins immediately and reaches high conversion after a few hours. In contrast, when a solution of $Cu(\mathbf{4a})_2$ (5 mol %) was added to a solution containing **1** and **2**, the reaction showed a substantial induction

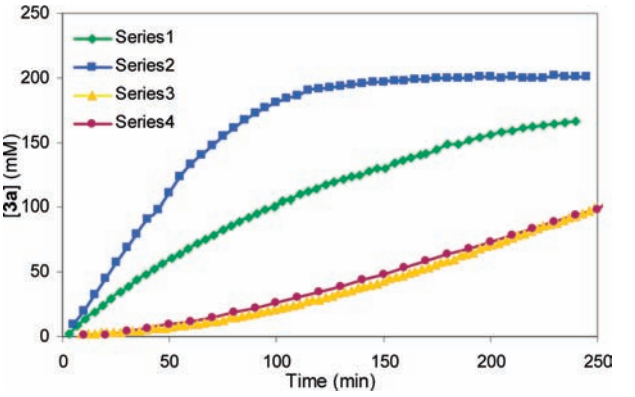


Figure 1. Monitoring the reaction of **1** and **2** by ^{1}H NMR. Series 1: 2.5 mol % Ag(I) added directly; Series 2: 5 mol % Cu(II) added after incubation with **2**; Series 3: 5 mol % Cu(II) added directly; Series 4: 5 mol % Cu(II) added after incubation with **1**.

period (Figure 1, series 3). As both **1** and **2** are capable of binding to Cu(II), we hypothesized that the induction period could be due to catalyst coordination with **1** or **2** to generate the "active" catalyst. When **1** and $Cu(\mathbf{4a})_2$ were combined and stirred at room temperature for 2 h and then added to a solution containing **2**, a similar induction period was observed (Figure 1, series 4). However, when a solution of **2** and $Cu(\mathbf{4a})_2$ was prestirred for 2 h and then added to **1**, no induction period was observed and the alkyne starting material was completely consumed in less than 3 h (Figure 1, series 2).

Based on these observations, we posited that the active catalyst for the reaction is a copper-indole complex and that formation of this complex under catalytic conditions is responsible for the induction period observed. The formation of this species can be observed by high-resolution mass spectrometry and UV−visible spectroscopy. A UV−visible spectrum of a solution of **2** and $Cu(\mathbf{4a})_2$ that was stirred at room temperature for 1 h shows a new peak in the visible region at 373 nm, which is considerably red-shifted from that of **2** or $Cu(\mathbf{4a})_2$ (see Supporting Information, Figure S2). High resolution mass spectrometry of the same solution shows a new peak at 930.37 *m*/*z*, corresponding to a complex with a copper/indole/phosphate ratio of 1:1:1. Under the catalytic conditions, two copper-containing peaks are observed at 814.30 and 1127.46 *m*/*z* by mass spectrometry, corresponding to copper(II) monophosphate and copper(II) monophosphate bound to both **1** and **2**, respectively. Additionally, the lack of nonlinear effects in the $Cu(\mathbf{4a})_2$-catalyzed reaction of **1** and **2** is consistent with the presence of a single chiral phosphate at the copper center during the enantiodetermining step (see Supporting Information, Figure S3). Taken together, these observations suggest that the copper-indole species is important for catalysis. Though we have no direct evidence for the mode of binding of indole to copper, we believe that a complex like **7** (Scheme 2), derived from electrophillic metalation of the $Cu(\mathbf{4a})_2$, is likely, as other late metal-indole complexes where binding occurs via the C3 position of indole have been reported.[15]

In our initial studies, we observed that 2-methyl indole (**6**) reacted very slowly with **1** (Table 2, entry 16). In light of our mechanistic investigations, we postulated that the decreased reactivity of **6** might be attributed to the sluggish formation of the analogous copper-2-methylindole species under catalytic

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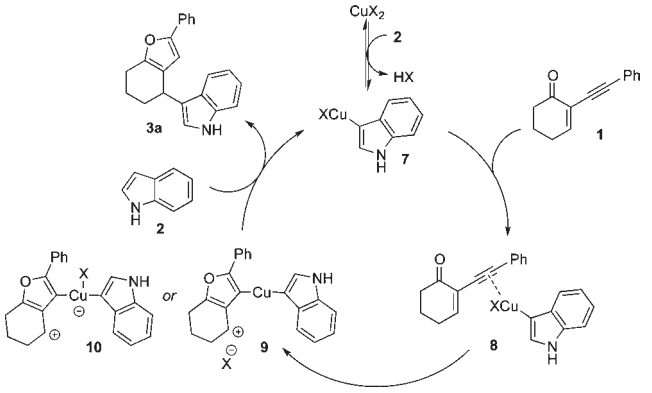
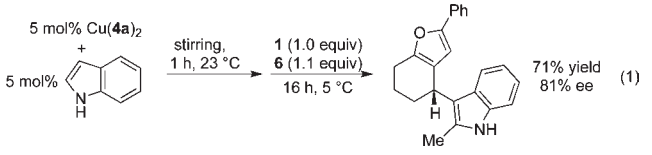
Scheme 2. Proposed Mechanism for the Cu(II)-Catalyzed Reaction of 1 and 2



conditions. Therefore, we hypothesized that the active copper-indole catalyst generated from **2** and Cu(**4a**)$_2$ would allow for improved reactivity with 2-methylindole. When 5 mol % of **2** and Cu(**4a**)$_2$ were combined in a 1:1 mixture for 1 h at room temperature and then added to a solution of **1** and **6** at 5 °C, a high conversion to **3p** was observed after only 16 h (eq 1). This experiment provides further support to our hypothesis that formation of a copper−indole complex is important for achieving catalysis.



A proposed mechanism consistent with our findings is shown in Scheme 2. Copper−indole complex **7** is formed when CuX_2 is combined with indole. In the catalytic cycle, this catalyst coordinates to the alkyne, forming intermediate **8**, which allows for addition by the carbonyl to generate a cuprated furan. The chiral phosphate could control the facial selectivity of the asymmetric nucleophilic attack on the carbocation through ion pairing in intermediate **9** or as an anionic ligand through cuprate **10**. Intermolecular nucleophile trapping is followed by protodemetalation to regenerate **7**.

In conclusion, we have demonstrated the first examples Ag(I)- and Cu(II)-mediated asymmetric cycloisomerization reactions triggered by π-activation in which the metal catalysts is devoid of ancillary L-type ligands.[16] The Cu(II)-catalyzed reaction shows a wide substrate scope and is tolerant to substitution on the indole and alkyne. Moreover, a copper−indole complex is proposed to be the active catalyst in the copper-catalyzed reaction, and incubation of CuX_2 and indole is vital to generating this species. Further work expanding the utility of these catalysts and concept to other types of metal-mediated asymmetric transformation is ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details including copies of NMR and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
fdtoste@berkeley.edu

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■ REFERENCES

(1) (a) Furstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (b) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. (c) Jimenez-Nunez, E.; Echavarren, A. *Chem. Rev.* **2008**, *108*, 3326–3350. (d) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371–384.

(2) (a) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104. (b) Lie, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198. (c) Lie, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472. (d) Mikami, K.; Kataika, S.; Yusa, Y.; Aikawa, K. *Org. Lett.* **2004**, *6*, 3699. (e) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (f) For use of a chiral diene ligand, see: Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumamoto, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1638.

(3) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018.

(4) (a) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850. (b) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (c) Toullec, P. Y.; Chao, C. M.; Chen, Q.; Gladiali, S.; Genet, J.-P .; Michelet, V *Adv. Synth. Catal.* **2008**, *350*, 2401. (d) Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinetti, A. *Org. Lett.* **2009**, *11*, 2137.

(5) (a) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 662. (b) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (c) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704.(d) (e) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *127*, 2764.

(6) (a) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988. (c) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem.—Eur. J.* **2009**, *15*, 1319. (d) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056. (e) Uemura, M.; Watson, I. D. G.; Katsukawa M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464. (f) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633. (g) Sethofer, S. G.; Meyer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.

(7) For (BINAP)Ag-catalyzed enantioselective carbostanylation of alkynes, see: Porcel, S.; Echavarren, A. *Angew. Chem., Int. Ed.* **2007**, 46.

(8) Trost., B. M.; Lee., D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.

(9) (a) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (b) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *122*, 608. (c) Aikawa, L.; Kojima, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6073.

(10) For use of late metal phosphates in asymmetric catalysis, see: **Ag**: (a) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (b) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984. **Pd:** (c) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. **Cu**: (d) Zhao, B.; Du, H.; Shi., Y. *J. Org. Chem.* **2009**, *74*, 8392. (e) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. **Fe**: (f) Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia, C.; Huang, H. *Chem.—Eur. J.* **2010**, *16*, 1638. **Rh**: (g) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987.

(h) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E; Doyle, M. P. *Tetrahedron Lett.* **1992**, *40*, 5983.

(11) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (c) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531.

(12) This intermediate has been intercepted by an enantioselective [3 + 3]-nitrone cycloaddition catalyzed by chiral phosphine−gold(I) complexes. Liu, F.; Qian, D. Y.; Li, L.; Zhao, X. L.; Zhang, J. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 6669.

(13) Notably, Cu(II)(**4a**)$_2$ is highly soluble in a variety of nonpolar organic solvents.

(14) The absolute stereochemistry of **3a** was assigned from its X-ray structure. The stereochemistry of the remaining products was assigned by analogy.

(15) Though both C2 and C3 electrophilic metalation are known, the C3 position is often metallated in the absence of protecting groups on N1 to favor the C2 position. For examples with **Cu**: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. **Pd**: (b) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. (c) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. **Hg**: (d) Kirby, G. W.; Shah, S. W. *J. Chem. Soc. Chem. Commun.* **1965**, 381. (e) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657.

(16) For an alternative strategy using copper salts/chiral Lewis base cooperative catalysis, see: Yang, T.; Farrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140.