Non-Precious Metals Catalyze Formal [4 + 2] Cycloaddition Reactions of 1,2-Diazines and Siloxyalkynes under Ambient Conditions

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Supporting Information

ABSTRACT: Copper(I) and nickel(0) complexes catalyze the formal [4 + 2] cycloaddition reactions of 1,2-diazines and siloxyalkynes, a reaction hitherto best catalyzed by silver salts. These catalysts based on earth abundant metals are not only competent, but the copper catalyst, in particular, promotes cycloadditions of pyrido[2,3-d]pyridazine and pyrido[3,4-d]pyridazine, enabling a new synthesis of quinoline and isoquinoline derivatives, as well as the formal [2 + 2] cycloaddition reaction of cyclohexenone with a siloxyalkyne.

The axially chiral 1,1′-binaphthalene-2,2′-diol (binol) has impacted asymmetric catalysis profoundly. Used widely as a chiral ligand and as a precursor to chiral ligands and catalysts, binol is best prepared by the oxidative dimerization of 2-naphthol. Binol derivatives, particularly those with substituents at the 3,3′-positions, allow fine-tuning of steric and electronic properties as well as sculpting of the scaffold’s chiral environment, thereby greatly enhancing the utility of this scaffold. Such 3,3′-disubstituted binols are nearly always made through a multistep sequence starting from a preformed binol, since the direct oxidative dimerization of 3-substituted naphthols is impractical given the limited availability of such naphthol precursors. Recently, we reported a general route to 3-substituted naphthol silyl ethers via a silver salt-catalyzed formal inverse electron-demand Diels−Alder (IEDDA) reaction between phthalazines and siloxyalkynes. Since phthalazines are prepared by a one-pot procedure from aromatic aldehydes, this cycloaddition methodology provides direct access to a variety of 2-hydroxynaphthalene derivatives, potential precursors to modified binol ligands (Scheme 1).

Nearly all reported IEDDA reactions of heterocyclic azadienes are thermal processes, typically requiring harsh conditions. Our interest in hydrogen-bonding catalysis prompted us to explore pyridinium salts designed to form two hydrogen bonds to the phthalazine nitrogen atoms as catalysts for the IEDDA reaction between phthalazine and electron-rich alkynes. The reaction with siloxyalkynes, while promoted by dual hydrogen bond donors, was catalyzed even by simple pyridinium salts and afforded, rather than the anticipated 2-naphthol derivative, an intriguing tetra-azapentacyclic compound, arising from a formal [2 + 2 + 2] cycloaddition between two phthalazines and a siloxyalkyne (Scheme 2, eq 1). Inspired by the ample precedent with normal electron demand Diels−Alder reactions, we evaluated various metals for promoting the desired IEDDA reaction and discovered that Ag(I) salts, especially when paired with bidentate N-donor ligands such as 2,2′-bipyridine and 1,10-phenanthroline, catalyzed the desired process to afford 3-substituted 2-naphthol.
silyl ethers in good yields (Scheme 2, eq 2). To make this strategy more versatile and practical, we have examined complexes of earth abundant metals as catalysts for the IEDDA reaction and report here that Cu(I) and Ni(0) complexes can supplant Ag(I) salts for these cycloadditions (Scheme 2, eq 3). Significantly, the copper salt catalyzes not only the cycloaddition of a broader range of substrates but also the [2 + 2] cycloaddition reaction between a siloxyalkyne and...
cyclohexenone, a transformation previously catalyzed by silver salts.\textsuperscript{13c}

The contrasting reactivity displayed by pyridinium salts and silver salts combined with a desire to identify non-precious metals for catalysis motivated us to examine a broader range of metal complexes for the IEDDA reaction of phthalazine (1) and 1-siloxyhexyne (2) (Table 1). Commonly employed Lewis acids, such as ZnBr\textsubscript{2}, TiCl\textsubscript{4}, Yb(OTf)\textsubscript{3}, Sc(OTf)\textsubscript{3}, Bi(OTf)\textsubscript{3}, Co(BF\textsubscript{4})\textsubscript{2}, La(OTf)\textsubscript{3}, In(OTf)\textsubscript{3}, and BF\textsubscript{4}·OEt\textsubscript{2} all failed to catalyze the reaction.\textsuperscript{18} Interestingly, while NiCl\textsubscript{2} was also ineffective, the corresponding Ni(0) complexes, Ni(PPh\textsubscript{3})\textsubscript{2} and Ni(ocl)\textsubscript{2}, afforded the desired cycloadduct in 21% and 43% yields, respectively (entries 1 and 2). This result suggests that the metal is not activating the diazine simply through Lewis acid/base interaction, since Ni(0) complexes are expected to be weakly Lewis acidic, certainly compared to NiCl\textsubscript{2}. We were pleased to find that Ni(CO)\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}, at 10 mol % catalyst loading, nicely catalyzed the cycloaddition at room temperature, affording the product in 80% yield (entry 3). Further addition of PPh\textsubscript{3} or P(OMe)\textsubscript{3} to the Ni(0) complex gave the product in diminished yields (entries 4 and 5). Isoelectronic with Ag(I) and Ni(0), Cu(I) salts were expected to also catalyze the cycloaddition reactions. Indeed, CuCl when used in conjunction with 2,2′-bipyridine did catalyze the reaction, albeit poorly (5% yield). The efficacy of Cu(I) salts improved with decreasing nucleophilicity of the counterion, as evidenced by increasing yields on going from CuI to CuCl to Cu(OTf). Even better results were obtained with highly dissociated counterions, such as PF\textsubscript{6} and BF\textsubscript{4} (entries 7–10). The best result was obtained using 10 mol % of tetrakis(acetonitrile)-copper(I) hexafluorophosphate with 2,2′-bipyridine as the ligand, which provided naphthalene in 80% isolated yield after 4 h reaction time (entry 11). Several other ligands were examined, but they did not better the yields (entries 12–15). Reactions proceeded in lower yields in acetonitrile and 1,4-dioxane, and no product was formed in chloroform or in protic solvents, such as methanol and water. The interchangeable use of silver, copper, or nickel complexes for the catalysis of these formal cycloadditions is noteworthy.\textsuperscript{17,19}

Having defined effective conditions for Cu(I)- and Ni(0)-catalyzed cycloaddition of the parent system, we next evaluated the substrate scope for the new catalyst systems (Figure 1). The two catalysts were expected to behave differently, since Ni(CO)\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} is hindered, having a sterically crowded neutral Ni(0) center, whereas Cu(I), as a soft Lewis acid, was expected to coordinate more strongly.\textsuperscript{20} Indeed, as noted above, while both provided silyl ether 3 in the same yield, the reaction was noticeably faster with the Cu(I) catalyst. Additionally, the two complexes displayed differing regioselectivities with unsymmetrical phthalazines. Whereas Cu(I) gave 1:1 mixture of the two regioisomeric products of 6-methoxyphthalazine, the Ni(0) catalyst gave 4 in a 1:5:1 preference over its regioisomer (not shown). A similar preference was observed with 5-chlorophthalazine and 5-fluorophthalazine, which produced naphthalenes 5 and 6, respectively, as the major products. In these instances, the slower reaction was also the more regioselective one. Other alkyl- and arylsiloxyalkynes were examined, and all gave the naphthalene products (7–9) in good yields. Benzo-fused derivatives of phthalazine enabled the synthesis of anthracene and phenanthrene derivatives. Thus, benzo[g]phthalazine gave anthracene products 10 and 11, whereas benzo[f]phthalazine gave phenanthrenes 12 and 13.

We had recognized early on that extending the IEDDA reactions to pyridopyridazines would open up a new route to quinolines and isoquinolines but had found the silver catalyst to be ineffective with most such substrates.\textsuperscript{21} We are delighted to note that this limitation can be overcome with the Cu catalyst. The reaction of pyrido[2,3-d]pyridazine and 1-siloxyhexyne (2), under standard Cu-catalysis conditions, gave small amounts of the quinoline product. When the same reaction was carried out in refluxing DCE, siloxyquinoline 16 was isolated in 41% yield, as a mixture of regioisomers.\textsuperscript{22} The related trifluoromethyl-substituted pyrido[2,3-d]pyridazine reacted smoothly at room temperature, thus affording the corresponding product mixture 17 in 64% yield.\textsuperscript{23} As observed with phthalazine (1), the reaction with the phenyl-substituted siloxyalkyne was more facile, giving the regioisomers of siloxyquinoline 18 in 74% yield. Similar success was enjoyed in the reaction between pyrido[3,4-d]pyridazine and phenyl-siloxyalkyne, which gave the regioisomeric isoquinoline products 19 in 67% yield.

The fruitful switch from a silver catalyst to a nickel or copper catalyst spurred a brief look at other reactions that might be amenable to such a change. Among the reactions of siloxyalkynes, we examined its formal [2 + 2]-cycloaddition with cyclohexenone, a transformation reported by Kozmin et al. to be catalyzed by AgNTf\textsubscript{2}.\textsuperscript{13c} Treatment of a solution of the two reactants with 5 mol % of Cu(MeCN)\textsubscript{5}PF\textsubscript{6} promoted its clean conversion to the [2 + 2]-cycloadduct (20), isolated in 74% yield (Scheme 3).\textsuperscript{24}

In conclusion, we have demonstrated that Cu(I) and Ni(0) complexes catalyze the formal [4 + 2] cycloaddition reactions of 1,2-diazines and siloxyalkynes to give silylo derivatives of naphthalene, anthracene, and phenanthrene. The copper catalyst was also effective in promoting the corresponding cycloaddition to generate quinoline and isoquinoline derivatives, as well as for the [2 + 2]-cycloaddition of siloxyalkyne and cyclohexenone. In more general terms, this study demonstrates the feasibility of switching from a precious metal to more economical, isoelectronic metals for catalyzing reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and copies of \textsuperscript{1}H and \textsuperscript{13}C NMR spectra for all new compounds being reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

Scheme 3. Cu(I) Catalysis of a formal [2 + 2] Cycloaddition Reaction of Siloxyalkynes

In Table 1 we observed that Cu(I) and Ni(0) complexes catalyze the formal [4 + 2] cycloaddition reactions of 1,2-diazines and siloxyalkynes to give silylo derivatives of naphthalene, anthracene, and phenanthrene. The copper catalyst was also effective in promoting the corresponding cycloaddition to generate quinoline and isoquinoline derivatives, as well as for the [2 + 2]-cycloaddition of siloxyalkyne and cyclohexenone. In more general terms, this study demonstrates the feasibility of switching from a precious metal to more economical, isoelectronic metals for catalyzing reactions.
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REFERENCES

(1) (a) Brunel, J. M. Chem. Rev. 2005, 105, 857. (b) Wang, H. Chirality 2010, 22, 827.

(2) For selected examples of oxidative dimerization of naphthols, see: (a) Guo, Q-X.; Wu, Z-J.; Luo, Z-B.; Liu, Q-Z.; Ye, J-L.; Luo, S-W; Sun, L-F.; Gong, L-Z. J. Am. Chem. Soc. 2007, 129, 13927. (b) Egami, H; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. J. Am. Chem. Soc. 2010, 132, 13633.

(3) Reviews: (a) Chen, Y.; Yekta, S.; Yudin, A. K. Chem. Rev. 2005, 105, 1801. (c) Shibasaki, M.; Matsunaga, S. Chem. Soc. Rev. 2006, 35, 269. (d) Pereira, M. M.; Calvete, M. J. F.; Carrilho, R. M. B.; Abreu, A. R. Chem. Rev. 2013, 62, 49690.

(4) For selected examples of binol derivatives in catalysis, see: (a) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. Angew. Chem., Int. Ed. 2004, 43, 5971. (c) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. J. Am. Chem. Soc. 2005, 127, 1336. (d) Li, G-Q.; Gao, H.; Keene, C.; Devonas, M.; Ess, D. H.; Kürti, L. J. Am. Chem. Soc. 2013, 135, 7414.

(5) A particularly important class of binol derivatives are chiral phosphoric acids: (a) Connon, S. J. Angew. Chem. Int. Ed. 2006, 45, 3909. (b) Terada, M. Synthesis 2010, 1929. For pioneering applications, see: (c) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Chem. Ing. Tech. 1999, 112, 3392. (d) Pereira, M. M.; Calvete, M. J. F.; Carrilho, R. M. B.; Abreu, A. R. Chem. Rev. 2013, 62, 49690.

(6) (a) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. J. Org. Chem. 2004, 2006, 116, 3392. (d) Pereira, M. M.; Calvete, M. J. F.; Carrilho, R. M. B.; Abreu, A. R. Chem. Rev. 2013, 62, 49690.

(7) Türkmen, Y. E.; Montavon, T. J.; Kozmin, S. A.; Rawal, V. H. J. Am. Chem. Soc. 2012, 134, 9062.

(8) Kessler, S. N.; Wegner, H. A. Org. Lett. 2012, 14, 3268.

(9) For reviews on the synthesis of substituted naptha[enes, see: (a) Kattzky, A. R.; Li, J.; Xie, L. Tetrahedron Lett. 1999, 55, 8263. (b) Rousseau, A. L.; de Koning, C. B.; van Otterlo, W. A. L. J. Org. Chem. 2004, 126, 5356.

(10) (a) Ting, M.; Li, J.; Xie, L. Tetrahedron Lett. 2005, 46, 4547. (d) Zhang, X.; Sarkar, S.; Larocq, R. C. J. Org. Chem. 2006, 71, 236. (e) Dai, Y.; Feng, X.; Liu, H.; Jiang, H.; Bao, M. J. Org. Chem. 2011, 76, 10068. (f) Xie, Y.; Qu, P.; Liu, Z.; Gu, R.; Xiao, Q.; Zhang, Y.; Wang, J. Angew. Chem. Int. Ed. 2013, 52, 2543. (g) He, Y.; Zhang, X.; Shen, N.; Fan, X. J. Org. Chem. 2013, 78, 10178.

(11) (b) Zhang, M.-Y.; Chan, C.-K.; Lin, S.-Y. Tetrahedron 2013, 69, 1532. (h) For reviews on the synthesis of substituted naptha[enes, see: (a) Boser, D. L. Tetrahedron 1983, 39, 2869. (b) Boker, D. L. Chem. Rev. 1986, 86, 781. (c) Foster, R. A. A.; Willis, M. C. M. Chem. Soc. Rev. 2013, 42, 63. For selected examples of Diels–Alder reactions of azadienes, see: (d) Selig, M. Org. Lett. 2010, 12, 4062. (e) Zagor, S. N.; Neuburger, M.; Wegner, H. A. Eur. J. Org. Chem. 2011, 3238. (f) Kessler, S. N.; Neuburger, M.; Wegner, H. A. J. Am. Chem. Soc. 2012, 134, 17885.