

Silver-Catalyzed Formal Inverse Electron-Demand Diels-Alder Reaction of 1,2-Diazines and Siloxy Alkynes

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S Supporting Information

ABSTRACT: A highly effective silver-catalyzed formal inverse electron-demand Diels–Alder reaction of 1,2-diazines and siloxy alkynes has been developed. The reactions provide ready access to a wide range of siloxy naphthalenes and anthracenes, which are formed in good to high yields, under mild reaction conditions, using low catalyst loadings.

 \neg he prominent role played by the Diels–Alder (DA) reaction in organic synthesis is due in no small measure to the discovery of Lewis acid catalysis of this reaction.¹⁻⁴ However, such activation has proven successful primarily for the acceleration of normal electron-demand DA reactions, those between electron-rich dienes and electron-deficient dienophiles. Lewis acid activation of the complementary process, the inverse electron-demand Diels-Alder (IEDDA) reaction, between an electron-deficient diene and an electronrich dienophile, has met with limited success.⁵ The IEDDA reaction of heterocyclic azadienes, including diazines,^{6,7} triazines,⁸ and tetrazines,⁹ provides access to a wide range of useful heterocycles and carbocycles.¹⁰ The reported IEDDA reactions of such azadienes are nearly all thermal processes, often requiring high reaction temperatures. For example, reactions of phthalazine with enamines or ynamines typically require heating to 130 °C or proceed only when electronwithdrawing groups are installed on the 1,2-diazines.^{6d} To the best of our knowledge, the only reported examples of Lewis acid-catalyzed IEDDA reactions of heterocyclic azadienes are those by Wegner and co-workers. These researchers employed a novel diboraanthracene for bidentate activation of phthalazine toward cycloadditions with enamines and enol ethers, allowing reactions to take place at 40-170 °C.^{11,12}

We describe the development of silver-catalyzed cycloaddition between phthalazines and siloxy alkynes,^{13,14} corresponding to a formal IEDDA reaction, that takes place with concomitant loss of nitrogen to afford a wide range of silylprotected 2-naphthols (eq 1).¹⁵ The reactions proceed at room temperature and give the products in good to high yields, typically using only 1.0–2.0 mol% of the Ag catalyst. It is noteworthy that 3-substituted 2-naphthols are important precursors to the widely used axially chiral 2,2'-binols.^{16,17}

In initial studies, we found phthalazine 1a to be unreactive toward siloxy alkyne 2a at room temperature and gave the expected cycloadduct in only 5% yield even after 24 h at 150 °C (0.2 M in mesitylene). Likewise, little or none of the



cycloadduct was observed when the reaction was carried out in the presence of common Lewis acids (MgCl₂, ZnBr₂, TiCl₄, $SnCl_4$, $Sc(OTf)_3$, and $BF_3 OEt_2$). The low reactivity observed with traditional Lewis acids prompted us to examine catalysts known to have π -acidic properties. Among the different metals considered, gold- and silver-based catalysts appeared promising, given their known high affinity for alkynes. When the reaction of 1a and 2a was carried out in the presence of 10 mol% AuCl, it produced the desired siloxy naphthalene 3a in 38% yield after 24 h at room temperature (Table 1, entry 1). The related gold salt [Au(PPh₃)NTf₂] also catalyzed the cycloaddition, albeit less effectively (14%). Better results were obtained with Agbased catalysts. The use of AgOTf (5 mol%) promoted a rapid reaction, giving the product in 57% yield (entry 2). The reaction conditions were developed further by taking into account the coordination chemistry of Ag complexes of diazines. The literature records examples of 1,2-diazines such as pyridazine and phthalazine functioning as non-chelating, bridging ligands for Ag⁺ ions, giving rise to polymeric complexes in some instances.¹⁸ Considering that such coordination of phthalazine to silver might be required for the observed reactivity, we hypothesized that a multidentate, chelating ligand might still enable the required activation but through a monomeric complex rather than polymeric or oligomeric structures. With that in mind, we examined *t*Bu-bipy 4 as a bidentate ligand and were pleased to see the yield rise to 79% (entry 3). Increasing the ligand:silver ratio to 2.2 did not affect the yield, but it slowed the reaction slightly. The reaction proceeded in lower yields in CH3CN and THF and was essentially shut down in ether and toluene. A further examination of ligands showed that BOX ligand 5 as well as the tridentate ligands pyBOX 6 and terpyridine 7 were lower yielding (entries 4-6). On the other hand, both bipyridine 8 and phenanthroline 9 were highly efficacious, affording the siloxy naphthalene product in 90 and 81% yields, respectively

Received: March 22, 2012







^{*a*}Reactions were carried out using 0.2 mmol of 1a and 0.3 mmol of 2a in CH₂Cl₂ (1.0 mL/0.1 mmol 1a). ^{*b*}Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^{*c*}1.0 mL of CH₂Cl₂/0.2 mmol 1a. ^{*d*}0.4 mmol of 1a was used. ^{*e*}0.4 mmol of 1a and 0.8 mL of CH₂Cl₂ were used. Abbreviations: TIPS, triisopropylsilyl; Tf, trifluoromethanesulfonyl; DMAP, 4-dimethylaminopyridine; TMEDA, tetramethylethylenediamine.

(entries 7 and 8). Further studies showed that pyridine and Hunig's base had almost no effect on the yield vis-à-vis the ligand free conditions (entries 9 and 10). Additionally, the strongly coordinating ligand DMAP stopped the activity of AgOTf completely when used in a 2.2:1 ratio (entry 11). Interestingly, the tertiary amine-based, bidentate ligand TMEDA proved to be highly effective, giving the product in 81% yield (entry 12). These results, when considered together, underscore the importance of bidentate chelating ligands for effective catalysis. Given its simplicity, bipyridine 8 was selected for further study. With 8 as the ligand, just 1 mol% loading of the AgOTf was sufficient to promote the reaction, providing the product in essentially the same yield as with 5 mol% loading (cf. entries 7 and 13). Comparable results were obtained, but with a shorter reaction time, when AgNTf₂ was used as the catalyst (entry 14).

We next investigated the scope of the catalyzed cycloaddition reaction under the optimized conditions (Table 2). Phthalazine and benzo[g]phthalazine gave the corresponding cycloadducts **3a** and **3b** in 82% and 72% isolated yields, respectively (entries 1 and 2). The latter result demonstrates that the current method can be applied equally to the preparation of siloxy anthracenes in addition to naphthalenes. Dichloro- and dimethyl-substituted phthalazines afforded the tetrasubstituted naphthalenes in good yields (entries 3 and 4). The reaction of

1-chlorophthalazine was highly regioselective, giving 3e as the only regioisomer (entry 5). 5-Nitrophthalazine gave the cycloadduct in good yield but with lower regioselectivity (entry 6). We have also examined the scope of the cycloaddition reaction with regard to changes in the substituents on the siloxy alkyne (entries 7-11). The sterically hindered tert-butyl-substituted siloxy alkyne reacted more slowly under the standard conditions but gave the expected product in good yield using 10 mol% of the catalyst in refluxing dichloromethane (entries 12 and 13). Siloxy alkyne having a phenyl substituent was particularly reactive and afforded the corresponding 3-phenyl-substituted naphthol product in 92% isolated yield with just 0.5 mol% catalyst loading (entries 14 and 15). The higher reactivity of the phenyl-substituted alkyne was confirmed through its reactions with other phthalazine derivatives. In all cases the corresponding products were obtained in high yields with 1 mol% catalyst loading (entries 16-18). It was found that pyridazine and pyrido[2,3d]pyridazine (10) gave no reaction when subjected to the above protocol.¹⁹ Finally, to assess the preparative value of the present cycloaddition methodology, we carried out the reaction between phthalazine 1a and siloxy alkyne 2a on a 20 mmol scale using 1 mol% of the catalyst and obtained the siloxy naphthalene product 3a in 74% isolated yield (5.26 g). To further demonstrate the scalability of the method, the tert-butylsubstituted siloxy alkyne was reacted with phthalazine 1a on a 10 mmol scale and gave the cycloadduct 31 in 83% isolated yield (2.97 g). It is noteworthy that 3-substituted 2-naphthols, prepared through this Ag-catalyzed process, are not readily accessible, as Friedel-Crafts reactions of 2-naphthols give 1substituted products with small electrophiles and a mixture of 3- and 6-substituted products with large electrophiles.²⁰

Scheme 1. Proposed Reaction Mechanism



A mechanistic rationale for the phthalazine-siloxy alkyne cycloaddition is presented in Scheme 1. One possibility is that silver ion coordination of the phthalazine renders it more electron-deficient, lowering the activation energy for a concerted IEDDA reaction (path A). We have found, however, that ethoxy alkyne 11 and ynamide 12, both of which are



comparably electron-rich to siloxy alkyne 2a, gave none of the expected cycloaddition products with phthalazine under the

Table 2.	Scope	of AgNTf.	-Catalyzed	Cycloaddition	Reactions ^a
	ocope	Of fight 12	2-Catary Zeu	Cycloaddition	Iccactions

			$R^2 R^3$ $R^1 $ N +		N⊤f ₂ , 8 F			S	
			R ¹	∏ rt, C R ⁴	CH ₂ Cl _{2 F}	²¹ 3a-p	R⁴		
Entry	Catalyst mol%	Time (h)	Product	Yield ^b (%)	Entry	Catalyst mol%	Time (h)	Product	Yield ^ь (%)
1	1.0	2	OTIPS	82	9	1.0	1	OTIPS	81
2	2.0	1.5	3a OTIPS	72	10 ^d	2.0	3		75
3	1.0	7		78	11 ^e	2.0	3		83
4	2.0	3	Me OTIPS	84	12 ^d	10	22	OTIPS	67 80
۲¢	2.0	4		67	13 /	1.0	1	3I OTIPS	80 95
3	2.0		3e	07	15	0.5	3	3m	92
6°	2.0	4	NO ₂ 3f (major)	74	16	1.0	3	OTIPS 3n	84
7 ^d	2.0	3	regioisomers 1.9:1	73	17	1.0	2		85
8 ^e	2.0	1	OTIPS OTIPS Ph 3h	70	18	1.0	6		94

^{*a*}Reactions were carried out using 0.5 or 1.0 mmol of diazine and 1.3 equiv of the siloxy alkyne with 8:AgNTf₂ ratio of 1.1:1. ^{*b*}Isolated yields. ^{*c*}For the determination of the regiochemistry of the product, see the Supporting Information. ^{*d*}2.0 equiv of siloxy alkyne was used. ^{*e*}1.5 equiv of siloxy alkyne was used. ^{*f*}The reaction was carried out in refluxing CH₂Cl₂.

same reaction conditions. These results, when considered with the ineffectiveness of the other Lewis acids tested (*vide supra*), suggest that the role of silver may not simply be to activate phthalazine. Indeed, ¹H NMR studies have previously shown that siloxy alkynes interact with AgNTf₂.^{13a} In light of these factors, one can also consider a stepwise mechanism to explain the formal cycloaddition reaction (path B). Coordination of the Ag⁺ to phthalazine²¹ and siloxy alkyne would not only bring the two reaction partners in proximity but also activate the two reactants. Nucleophilic attack of the siloxy alkyne to phthalazine would produce a diaza-enolate intermediate along with a highly reactive silylketenium. Intramolecular addition of the diaza-enolate to the silylketenium would give a bicyclic azo intermediate that, upon spontaneous extrusion of N₂, would afford the siloxy naphthalene product along with the initial catalyst.^{22,23}

In summary, we have developed a Ag-catalyzed formal inverse electron-demand Diels—Alder reaction of phthalazines with siloxy alkynes to afford a broad range of silyl protected 2naphthols. The cycloadditions proceed at room temperature and give the products in good to high yields, typically with just 1.0-2.0 mol% catalyst loadings. We believe that the catalysis of IEDDA reactions of various other heterocyclic azadienes presents a fertile ground for the discovery of useful new synthetic methods.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and full compound characterization. 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.

ACKNOWLEDGMENTS

This work was funded by the National Institutes of Health (P50 GM086145) and the Chicago Biomedical Consortium with support from the Searle Funds at the Chicago Community Trust.

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between phthalazines and siloxy alkynes. These findings will be reported in due course.