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Gallium(III)-Promoted Halocyclizations of 1,6-Diynes

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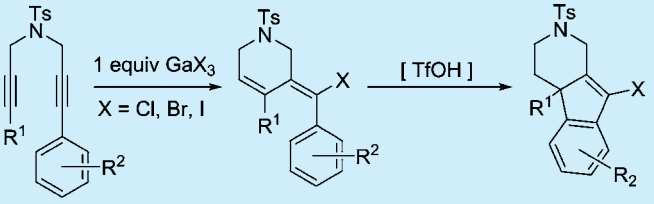
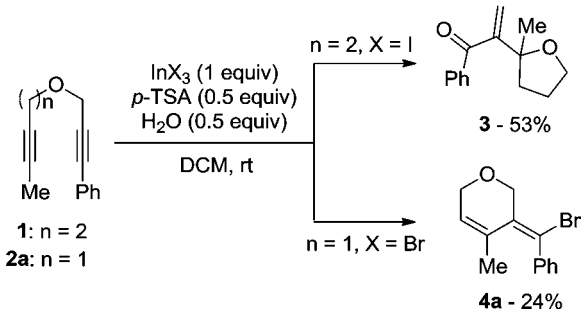
Supporting Information

ABSTRACT: Cyclization of 1,6-diynes promoted by stoichiometric Ga(III) halides produces vinyl halides in good to excellent yields. Under acidic conditions, initially formed iodocyclization products undergo in situ Friedel–Crafts cyclizations, giving access to iodoindenopyridines. Application of the vinyl halides in cross-coupling reactions has been explored, and mechanistic aspects of the cyclization are discussed.



π-Lewis acid promoted cyclizations have become a highly productive field of research in the development of new synthetic methodologies.[1] In an earlier investigation, we reported the use of stoichiometric In(III) as a π-Lewis acid catalyst to promote cyclization of 1,7-bisalkynyl ethers to tetrahydrofuranyl enones (Scheme 1, top).[2] We noted at the time that decreasing the tether length between the two alkynes by a single methylene to 1,6-bisalkynyl ether **2a** resulted in a modest conversion to dihydropyranyl vinyl bromide **4a** in low isolated yield (Scheme 1, bottom). Given the broad utility of vinyl halides in natural product synthesis[3] and drug development,[4] we began developing this chemistry as a route to new scaffolds for the production of small-molecule libraries. Herein we report a method to construct several vinyl halide scaffolds in moderate to excellent yields from simple starting materials, using readily available Ga(III) halides as reagents.

Scheme 1. Divergent Cyclization Catalyzed by In(III)



In comparison to the considerable effort directed toward exploiting the π-acidity of the noble metals in the past several decades,[5] the catalytic applications of In(III) and Ga(III) have only recently begun to garner interest. Perhaps this is due, in part, to the fact that they do not have an obvious catalytic niche, being both competent σ- and π-acids. As the former, they have both been shown to be potent oxophiles activating ketones and aldehydes, carboxylic acids, amides, epoxides, and ethers to a range of nucleophilic additions.[6] As the latter, they have been used as competent ynophiles activating alkynes in hydroaminations,[7] hydroarylations,[8] and ene-yne reactions.[9] Of particular relevance to this work, InI_3[10] and $GaCl_3$[11] have recently been reported as effective catalysts for cationic polycyclizations initiated by alkynes. Despite these substantial efforts, yne-yne cyclizations have remained unexplored, and to the best of our knowledge, this is the first report of a halogenative cyclization involving GaX_3 or InX_3.[12] Work by Yu reported a related oxocarbenium ion-initiated bisalkyne halocyclization triggered by Fe(III) halides.[13]

Initial efforts to increase the yield of the In(III)-catalyzed halogenative cyclization (Scheme 1) were met with limited success. Attempts at optimization, including changes in solvent,[14] temperature, and concentration proved fruitless in increasing the yield beyond 30%. The persistently low yields were found to be primarily attributable to the instability of vinyl bromide **4a**, with decomposition occurring during the relatively long reaction times required for conversion (>12 h) and subsequent purification. Given the ability of Ga(III) to promote ring-opening polymerization reactions of cyclic ethers,[15] *N*-tosylate (NTs)-tethered diynes were examined as potentially more stable substrates.

The NTs-linked substrates proved fruitful, and bisalkyne **2b** was converted to vinyl bromide **4b** with an 80% isolated yield (Table 1, entry 1). Screening related π-acids revealed In(III) chloride and iodide to be suitable catalysts, and the corresponding vinyl chloride **5b** and iodide **6b** were isolated in good to excellent yields (Table 1, entries 2 and 3). The reaction times increased in the series InI_3 < $InBr_3$ < $InCl_3$, with the chloride requiring refluxing in dichloroethane (DCE) to complete the reaction in 12 h. Both In(III) triflate with added bromide and In(I) bromide were ineffective at promoting any reaction. In an effort to accelerate the reaction, Ga(III) was then examined as a promoter.

Gallium(III) was found to promote the reaction at a faster rate, and with $GaBr_3$, vinyl bromide **4b** could be isolated nearly

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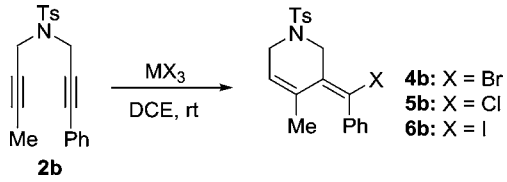
Table 1. Halocyclization Catalyst Optimization



entry	MX_3	catalyst (equiv)	time (h)	yield (%)[a]
1	$InBr_3$	1.0	36	80
2	$InCl_3$	1.0	12	72[b]
3	InI_3	1.0	3	93
4	InBr	1.0	24	0
5	$GaCl_3$	1.0	1	55
6	$GaBr_3$	1.0	0.5	95
7	GaI_3	1.0	0.2	88
8	$GaBr_3$	0.2	2	76[c]
9	GaI_3	0.2	5	56[d]

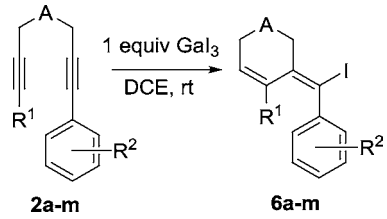
[a]Isolated yield. [b]Run at 84 °C. [c]Run at 50 °C, with 1.0 equiv of TMSBr. [d]Run with 1.0 equiv of TMSI.

quantitatively in 30 min. Conversion to the vinyl chloride **5b** and vinyl iodide **6b** also proceeded smoothly, with GaI_3 affording complete conversion to the corresponding vinyl iodide in less than 10 min (Table 1, entries 7–9). As with In(III) promoters, the rate of the reactions increased in the series I > Br > Cl.

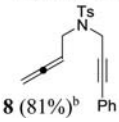
A variety of halide sources and conditions were screened in an attempt to render the Ga(III) catalyst substoichiometric. These included additives such as halide salts (TBAB, NaBr, KI), acid halides (HBr, HI, pyridinium hydrobromide), and halosilanes (TMSBr, TMSI), as well as $Ga(OTf)_3$ and $In(OTf)_3$ with added bromide or other nucleophile traps. Only the halosilanes gave any catalyst turnover, and vinyl bromide **4b** or iodide **6b** could be isolated in 76 and 56% yield, respectively, with 20 mol % catalyst and stoichiometric halosilane (Table 1, entries 8 and 9). Given the decrease in yield, more difficult purification, comparable cost of the gallium salts relative to the halosilanes, and a turnover number of only 3, stoichiometric Ga(III) halides were used in subsequent studies.

The range of diynes amenable to this chemistry was then explored using GaI_3 (Table 2). Consistent with previous observations, etherate **2a** (Table 2, entry 1) gave a lower yield of vinyl idoide **6a** in comparison to the *N*-toslyate **2b**. Accordingly, we focused our efforts on *N*-tosylates. Terminal alkynes excluded (Table 2, entry 2), a wide range of arylalkynyl substrates proved amenable to the reaction, and smooth conversion to the desired products was observed for most (Table 2, entries 3–10). Despite excellent conversions (80–94%), some of the products were unstable to silica gel chromatography, resulting in significant loss of material (Table 2, entries 2, 8, 9, and 10). Fortunately, basic extractive workup was effective at purifying the vinyl halides to >91% purity, and these products could be used in further cross-coupling chemistry as the near pure material (vida infra). The relative rate of the cyclizations showed a dependence on the electron-richness of the arylalkyne. Electron-rich substrates (Table 2, entries 4 and 5) gave near immediate conversion to product, while electron-withdrawing groups slowed the reaction considerably (Table 2, entries 7–10). In the case of benzoate **2i** and nitrobenzene **2k**, mild heating was effective in decreasing the reaction time. *β*-Trimethylsilyl-substituted alkyne **2m** gave only the desilylated allene **8** on treatment with catalyst (Table 2, entry 12).

Table 2. Iodocyclization Substrate Scope



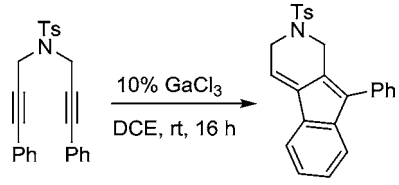
2a-m **6a-m**

entry	diyne	A	R^1	R^2	time (h)	prod. (NMR yield, yield[a])
1	**2a**	O	Me	H	0.5	**6a** (71%, 30%)
2	**2c**	NTs	H	H	24	N/A (0%)
3	**2d**	NTs	Et	H	0.8	**6d** (80%, 53%)
4	**2e**	NTs	Me	*p*-OMe	0.1	**6e** (93%, 88%)
5	**2f**	NTs	Me	3,5-Me	0.2	**6f** (94%, 93%)
6	**2g**	NTs	Me	*m*-OMe	0.8	**6g** (94%, 87%)
7	**2h**	NTs	Me	*p*-Cl	0.8	**6h** (92%, 78%)
8	**2i**	NTs	Me	*p*-CO_2Me	9[b]	**6i** (88%, 36%)
9	**2j**	NTs	Me	*p*-CF_3	2	**6j** (88%, 61%)
10	**2k**	NTs	Me	*p*-NO_2	3	**6k** (83%, 45%)
11	**2l**	NTs	Ph	H	0.2	**6l** (41%, 41%)
12	**2m**	NTs	CH_2-$SiMe_3$	H	2[c]	 **8** (81%)[b]

[a]Isolated yield. [b]Run at 60 °C. [c]Run with 10 mol % of $GaCl_3$.

Diphenyl diyne **2l** (Table 2, entry 11) gave the expected product **6l** only in relatively low yield (41%), the major product being tricyclic scaffold **7**, isolated in 46% yield. The use of $GaCl_3$ was effective in increasing the yield of **7** to 82%, requiring only 10 mol % catalyst (Scheme 2).

Scheme 2. Diphenyldiyne Cycloisomerization



2l **7** (82%)

The pathway to products **6** may follow an initial 6-*exo*-*dig* cyclization promoted by Ga(III) activation of diyne **A**, giving vinyl carbenium intermediate **B** (Scheme 3). Trapping of this vinyl carbenium ion by a halide from the Ga(III) promoter to vinyl gallate **C**, followed by protodegallation from adventitious water or during aqueous quench, delivers vinyl iodides **6**. Products were observed with the halide incorporated adjacent to the arene as the sole regioisomers. Given that both alkynes are potential *π*-bases, it is likely that this regioselectivity is driven by the stability of the vinyl cation **B**, favoring halogenation at the benzylic position. The increase in the reaction time observed with more electron-deficient arenes is thus rationalized by the

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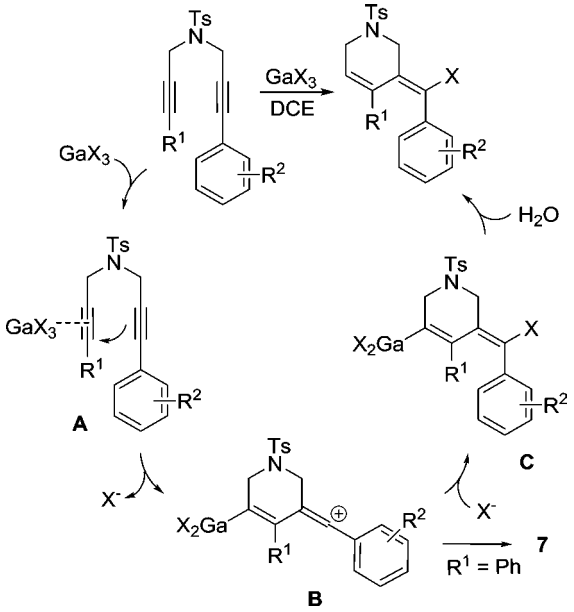
Scheme 3. Proposed Mechanism for the Formation of Products 6 and 7

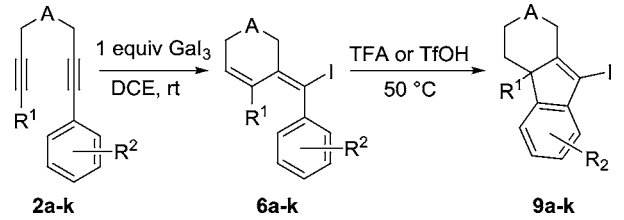


slower rate of formation of the higher energy vinyl carbenium intermediate due to increased electron withdrawal on the aryl ring.

Satisfyingly, this mechanism also anticipates the formation of **7** from **2l** as the diphenyl system contains an arene nucleophile capable of trapping the vinyl cation via an intramolecular Friedel–Crafts reaction. The increase in the yield of **7** with 10 mol % of $GaCl_3$ is likely a consequence of the slower rate of chloride trapping of the vinyl carbenium, in comparison to iodide, allowing greater internal arene addition. Products such as **7** have also been observed with Au(I) catalysis.[16] We are currently further exploring this biscyclization with diaryl bisalkynes.

During optimization efforts for the formation of **6**, several additives were examined as proton sources to quench the vinyl gallate intermediate **C**. While not significant to the formation **6**, the addition of acid (TFA, HBr, and $Ga(OTf)_3$) gave small amounts of indenopyridine **9b** (Table 3, entry 2). This product was presumed to be the result of a Bronsted acid catalyzed intramolecular Friedel–Crafts alkylation of the carbenium ion formed upon protonation of the endoalkene of the vinyl iodide **6**. Attempts to favor this process by the addition of TFA to the halocyclization products formed in situ were successful. *N*-Tosyl diyne **2b** could be converted to indenopyridine **9b** in a two-step, one-pot procedure with a 91% overall yield by adding TFA to the reaction mixture once thin-layer chromatography analysis had determined that all of the starting diyne **2b** had been converted to **6b** (Table 3, entry 2). This procedure was effective at further cyclizing several of the *N*-tosylate diynes **6** to **9** (Table 2, entries 5 and 7). However, some of the substrates decomposed under these reaction conditions at rates comparable to the formation of the desired product. Surprisingly, a two-step procedure where the vinyl iodide **6** was isolated and then subjected to TFA without GaI_3 present afforded no reaction.[17] Presumably, TFA was acting to liberate HI from GaI_3, and the stronger acid was necessary for protonation. Triflic acid provided a convenient solution, and the crude vinyl iodides **6** could be converted to **9** with superior yields by treatment with this acid after removal of

Table 3. Tandem Iodocyclization/Friedel–Crafts Scope



entry	diyne	A	R^1	R^2	product (% yield)[a]
1	**2a**	O	Me	H	N/A (0[b], 0[c])
2	**2b**	NTs	Me	H	**9b** (91[b])
3	**2d**	NTs	Et	H	**9d** (66[b], 73[c])
4	**2e**	NTs	Me	*p*-OMe	**9e** (0[b], 58[c])
5	**2f**	NTs	Me	3,5-Me	**9f** (91[b])
6	**2g**	NTs	Me	*m*-OMe	**9g** (29[b], 52[c])
7	**2h**	NTs	Me	*p*-Cl	**9h** (97[b])
8	**2i**	NTs	Me	*p*-CO_2Me	**9i** (20[b], 33[c])
9	**2j**	NTs	Me	*p*-CF_3	**9j** (25[b], 48[c])
10	**2k**	NTs	Me	*p*-NO_2	N/A (0[b], 0[c])

[a]Isolated yield. [b]One-pot procedure with TFA. [c]Two-step procedure with TfOH.

GaI_3 via basic workup in a two-step sequence (Table 3, entries 3, 4, 6, 8, and 9). Dipropargyl ether **2a** gave only a trace conversion to the desired indenopyran, decomposing under all conditions. In addition, **2k** failed to react even at high temperatures, stopping at the vinyl bromide **6k** likely due to the low nucleophilicity of the nitroarene.

The vinyl halides **9** were more stable than their exocyclic vinyl halide counterparts **6** and could be chromatographed in silica gel and stored for months without noticeable decomposition.

With access to a range of vinyl iodides **6** and **9**, the utility of these structures in selected cross-couplings was then examined (Figure 1). Under standard unoptimized conditions, Suzuki and Sonagashira couplings produced the corresponding arylated and alkynyl products, respectively, in fair to excellent yields.

Despite the relatively short shelf life of the vinyl halides **6**, these cyclization products proved to be useful in Suzuki cross-couplings without the need to purify the vinyl halides, as evidenced by compounds **10c** and **10i**. The two-step isolated

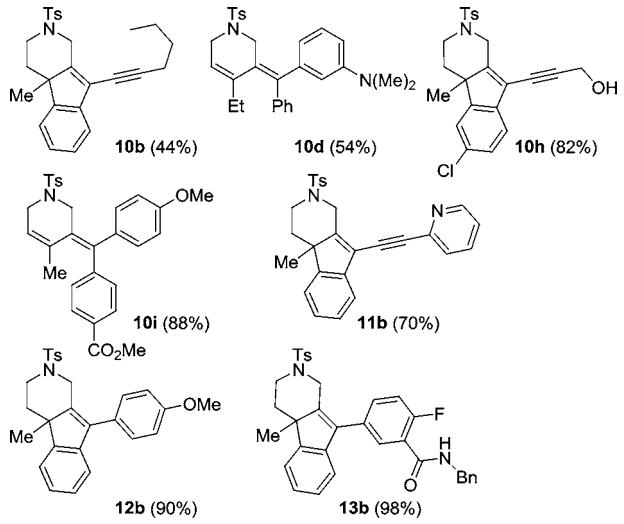


Figure 1. Cross-coupling products of vinyl iodides.

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yield of the cross-coupled products prepared from the crude vinyl iodide far exceeded the isolated yields of the first step.

In conclusion, we have developed a simple method for the construction of iodotetrahydropyridines and indenopyridines using GaI_3 and have shown that these products are capable substrates in cross-coupling reactions. These reactions offer quick access to easily diversifiable scaffolds from simple starting materials via a previously unreported mechanism wherein GaX_3 acts to promote a diyne cyclization and is a halide source. We are now expanding on the cross-coupling reactions to produce a library for biological screening.

■ ASSOCIATED CONTENT

Supporting Information

General experimental protocols and characterization data for all compounds. 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.

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(14) Coordinating solvents (ACN, THF, DMF) returned starting material, whereas noncoordinating solvents (DCE, chlorobenzene, $CHCl_3$) behaved similarly. DCE was chosen out of convenience.

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(17) Subjecting isolated **6** to the reaction conditions with both GaI_3 and TFA did bring about conversion to **9**.

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