HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1184-1196. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 2nd September, 2016, Accepted, 14th November, 2016, Published online, 16th February, 2017
DOI: 10.3987/COM-16-S(S)67

HALOCYCLIZATIONS AND CYCLOISOMERIZATIONS OF BISARYL 1,6-DIYNES

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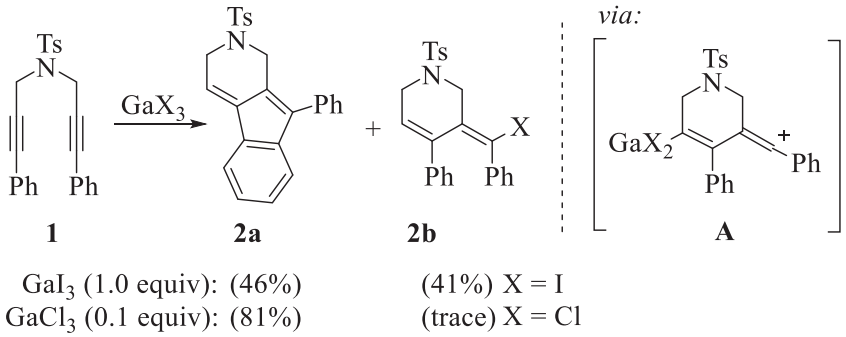
Abstract – *N*-Sulfonamide tethered bisaryl 1,6-diynes underwent cyclization in the presence of Ga(III) trihalide to give mixtures of halocyclization (HC) and Friedel-Crafts (FC) cycloisomerization products. The ratio of products was found to be dependent on the identity of the halide and diyne substrate. In contrast, under Bronsted acid conditions only Friedel-Crafts cycloisomerization products were obtained. The regiochemical preference of the cyclization under Bronsted acid catalysis was reversed under Lewis acid catalysis. Herein, we report our efforts to understand and make use of this disparity to access a range of vinyl halides and indenopyridines from readily accessible 1,6-diynes.

Chemists have long been motivated to develop methods for the formation of cyclic ring systems as relevant substructures in many bioactive small molecule drugs and natural products.[1] Metal-catalyzed carbocyclizations of 1,*n*-enynes have been widely exploited for this purpose, functioning as accessible acyclic precursors to many novel carbo- and heterocyclic frameworks.[2] Cycloisomerizations of bisaryl 1,*n*-diynes have received less attention.[3] Unlike enynes, where cyclization is predictably initiated at the alkyne, 1,*n*-diynes have the potential to generate regioisomeric mixtures depending on which alkyne is activated by the catalyst.

The ability of Ga(III) to function as a π-Lewis acid for the activation of alkynes is a growing field that has received considerable attention in recent literature; cyclizations initiated at alkynes have been shown for enynes, allenynes, arylynes, and polyenes.[4] We recently reported a study of GaX_3 promoted halocyclizations of 1,6-diynes which presumably proceeded through the involvement of GaX_2^+.[5,6] We had noted at the time, the reaction of bisaryl diyne **1** with stoichiometric GaI_3 gave a near 1:1 mixture of tricyclic indenopyridine **2a** (46%) along with the expected halocyclization product **2b** (41%) (Scheme 1). The production of **2a** was rationalized as a consequence of an intramolecular Friedel-Crafts closure onto

an intermediate vinyl cation **A** competing with the external trapping of **A** by iodide. Accordingly, using only 10 mol% $GaCl_3$, indenopyridine **2a** was obtained in 81% yield with only trace vinyl chloride detected.



Scheme 1

Analogous polycyclizations of 1,6-diynes wherein cycloisomerization occurs with the intervention of an internal nucleophile have been shown for electrophilic promotors such as I_2,[7] and $IPyBF_4$,[8] and Lewis acid catalysts such as Au(I)[9] and $FeCl_3$.[10] Liu and coworkers have developed an efficient $AuCl(PPh_3)/AgSbF_6$ catalyzed reaction capable of the same transformation depicted in Scheme 1, **1** was converted to **2a** in 61% yield.[11] The authors reported superior yields with *O*-tethered diynes, but note that unsymmetric bisaryl diynes gave nearly equal mixtures of the two regioisomeric products. Herein, we report our efforts to apply Ga(III) Lewis acid promoted cyclizations to unsymmetric bisaryl 1,6-diynes, and compare the regiochemical preference to a Bronsted acid catalyzed transformation discovered in the course of this investigation. *N*-Tosyl tethered 1,6-diynes were chosen as a model system as earlier work indicated these substrates were particularly well behaved.[5]

In the reaction of an unsymmetric bisaryl diyne with GaX_3 catalyst, four possible products were expected corresponding to two possible chemoselectivities and two possible regioselectivities. Figure 1 depicts these pathways: initial π-coordination of GaX_2^+ to either alkyne prompts a 6-*exo*-dig cyclization to generate either of two regioisomeric vinyl carbocations (Figure 1, **AB** and **CD**). Internal trapping of those cations by the neighboring arene, followed by rearomatization and protodegallation, affords the two Friedel-Crafts (FC) products, **a** and **c**. Trapping by an external halide, affords the halocyclization (HC) products, **b** and **d** (Figure 1).

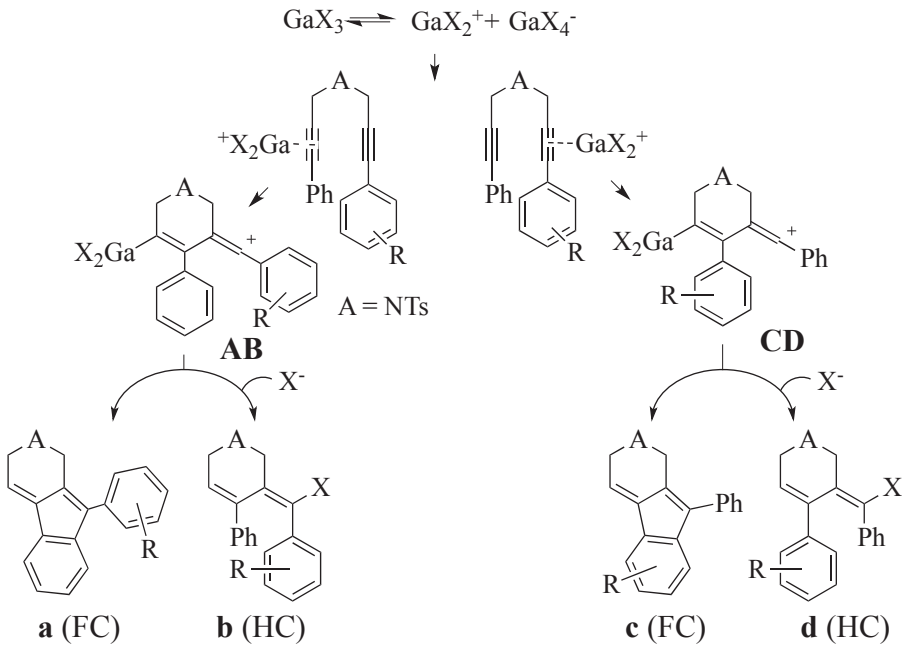


Figure 1

Initial efforts to optimize the FC pathway focused on removal of the nucleophilic halide counterion of the Ga(III) catalyst, anticipating that this would prevent the competing halocyclization and afford solely the FC products, **a** and **c**. Given the non-nucleophilic counterion, Ga(III) triflate seemed an attractive catalyst. However, under a range of conditions no reaction was observed (Table 1, entry 1, other aprotic solvents not shown). It was presumed that generating the $Ga(OTf)_2^+$ cation is unlikely in the absence of stabilizing ligands. In the presence of $Ga(OTf)_3$ and non-nucleophilic protic solvents such as hexafluoroisopropanol (HFIP) or TFA, diyne **1** was converted to indenopyridine **2a** in 25% and 55% yields respectively (Table 1, entries 2 and 3). Little reaction was observed with less acidic AcOH as the solvent (Table 1, entry 4). The possibility that the combination of $Ga(OTf)_3$ and protic solvent was simply acting as a source of triflic acid was then explored. A control experiment using triflic acid in place of $Ga(OTf)_3$ revealed the Bronsted acid to have similar activity and the desired product **2a** was obtained with an improved yield (80%) in comparison to the Ga(III) catalyzed reaction (Table 1, entry 5). Optimal conditions using triflic acid as the initiator benefited from the use of TFA as the solvent. Switching to AcOH or DCE gave slow conversion to complex mixtures with significantly diminished yields (Table 1, entries 6 and 7), while THF was not compatible with the triflic acid catalyst (Table 1, entry 8). Trifluoroacetic acid alone was unable to catalyze the reaction (Table 1, entry 9). This Bronsted acid catalyzed reaction can

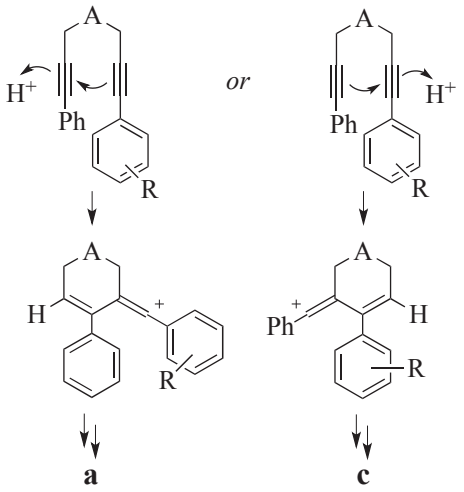
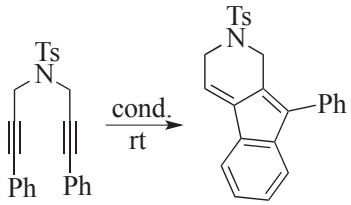


Figure 2

Table 1. Optimization 1,6-Diyne FC Cycloisomerization



1 **2a**

entry	catalyst (mol%)	solvent	conversion to **2a** (%)[a]
1	$Ga(OTf)_3$ (100)	DCE	0
2	$Ga(OTf)_3$ (100)	HFIP	25
3	$Ga(OTf)_3$ (20)	TFA	55
4	$Ga(OTf)_3$ (20)	AcOH	<5
5	TfOH (20)	TFA	80[b]
6	TfOH (20)	AcOH	35
7	TfOH (20)	DCE	45
8	TfOH (20)	THF	0
9	None	TFA	0

[a]Assessed from NMR of crude reaction mixtures [b]Isolated yield

potentially be understood in a similar way to the Ga(III) promoted reaction (Figure 1 above), with protonation of the alkyne initiating the chemistry *in lieu* of Lewis acid coordination (Figure 2).

Using these halide-free Bronsted acid conditions, the regioselectivity of the reaction with unsymmetric bisaryl diynes was assessed and compared to GaI_3 catalysis (Table 2). As expected, under Bronsted acid conditions (TfOH/TFA), a mixture of two regioisomers arising from protonation of either alkyne was produced (Table 2, **a** and **c**). For strongly activated *p*-methoxy substituted arene **3** an intractable mixture resulted (Table 2, entry 1). For 3,5-dimethylphenyl substituted diyne **4**, a 1:15 mixture of products (**8a**:**8c**) was obtained (Table 2, entry 2). The major product **8c** was isolated in 80% yield. This regiochemical outcome indicates the more electron rich dimethylphenyl substituted alkyne had been preferentially protonate d to initiate the first cyclization, and subsequently the more electron rich aryl ring had served as the Friedel-Crafts nucleophile. Notably, for this electronically activated substrate, TfOH was not required and the reaction progressed in the TFA solvent alone. For *m*-methoxyphenyl substituted diyne **5**, a 7:3 mixture of pro ducts (**9a**:**9c**) was produced (Table 2, entry 3). Strikingly, the major product **9a**, isolated in 52% yield, indicates the unactivated phenyl acted as the Friedel-Crafts nucleophile over the electronically activated *m*-methoxyphenyl. Considering the *m*-methoxyphenyl would presumably decrease the basicity of the appended alkyne (σ_{meta} = 0.115),[12] the primary factor controlling the regioselectivity of these Bronsted acid catalyzed cyclizations is likely the initial site of alkyne protonation (Figure 3). Arenes substituted with the electron withdrawing groups *p*-CO_2Me and *p*-CF_3 supported this conclusion, giving single detectable regioisomers **10a** and **11a** which could be isolated, in 63% and 90% yield respectively (Table 2, entries 4 and 5). In both cases, initial protonation would be expected to occur on the more electron-rich phenyl substituted alkynes, leading to the observed products.

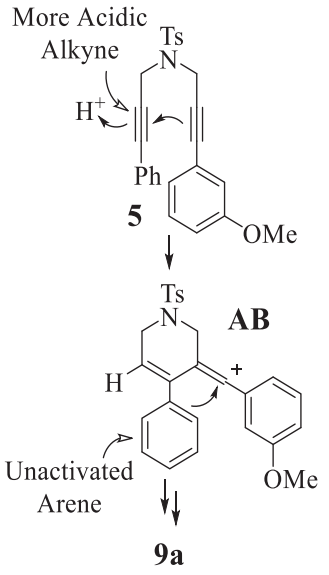
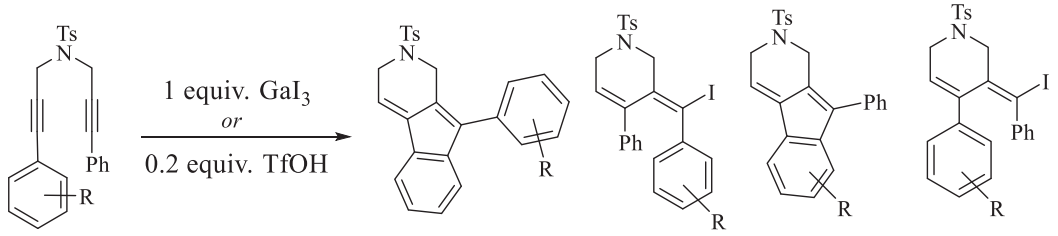


Figure 3

Table 2. Regio- and Chemoselectivity of Bisaryl 1,6-Diyne Cyclizations



3-7 **8-11a** **8-11b** **8-11c** **8-11d**

			Bronsted Acid Conditions[a]		**GaI_3 Conditions**[b]	
entry	diyne	R	r.r. (**a**:**c**)[c]	major prod. (% yield)[d]	r.r. (**a**:**b**:**c**:**d**)[c] (**a**+**b**:**c**+**d**)	major prod. (% yield)[d]
1[e]	**3**	*p*-OMe	NA	complex (0)	NA	complex (0)
2[e]	**4**	3,5-Me	1:15	**8c** (80)	15:34:51:0 49:51	**8c** (45)
3	**5**	*m*-OMe	7:3[f]	**9a** (52)	25:18:57[f]:0 41:57	**9c** (29)
4	**6**	*p*-CO_2Me	20>1[g]	**10a** (63)	30:0:14:56 40:60	**10d** (48)
5	**7**	*p*-CF_3	20>1[g]	**11a** (90)	26:0:0:74 26:74	**11d** (55)

[a]0.2 equiv. TfOH in 0.1 M TFA [b]1 equiv. GaI_3 in 0.2 M DCE [c]Product ratios determined from NMR integrations of crude reaction mixtures [d]Isolated yields of major products [e]Run in 0.1 M TFA without added TfOH [f]Mixture of two isomers: C6-methoxy **9c'**, and C8-methoxy **9c''**. [g]Minor regioisomers were not detected at the limit of the NMR.

The regio- and chemoselectivity of these substrates under Ga(III) promoted cyclization conditions was then assessed (Table 2). On treatment with GaI_3 mixtures of up to 4 products are possible: two halocyclization products (**b** and **d**) arising from iodine trapping of the proposed vinyl cation intermediates (Figure 1, **AB** and **CD**), and two FC products (**a** and **c**) arising from arene trapping of the same intermediates (Figure 1). Summing the yields of the two products presumed to arise from each vinyl cation (**a**+**b**:**c**+**d**) gives a measure of the regioselectivity (r.r.) of the initial cyclization step (Table 2). Like the Bronsted acid catalyzed reaction, *p*-methoxyphenyl substituted diyne **3** gave a complex mixture on treatment with GaI_3 (Table 2, entry 1). 3,5-Dimethylphenyl substituted diyne **4** gave a mixture of three products with no apparent regioselectivity in the initial cyclization step (49:51). The two observed products (**8a** and **8b**) presumed to arise from carbocation **AB** (Figure 1) comprised 49% of the mixture, while the single observed product (**8c**) presumed to arise from intermediate CD comprised 51% of the mixture. It is understandable that HC product **8d** was not detected, as the intramolecular trapping of vinyl cation **CD** via the FC pathway is likely to be fast for the electronically activated 3,5-dimethylphenyl nucleophile in comparison to the intermolecular iodide trap. For *m*-methoxyphenyl substituted diyne **5** a

slight regiochemical preference (41:57) for products presumed to arise from the **CD** cation were found to predominate (Table 2, entry 3). Surprisingly, this selectivity is the reverse of our observations with triflic acid promoted catalysis, which gave a 7:3 selectivity favoring the other regioisomeric pathway. This result can be explained if the Ga(III) catalyzed process favors formation of the presumed more stable vinyl carbocation as opposed to protonation of the more electron rich alkyne (Figure 4). As electron withdrawal on one of the alkynes increased, this disparity became more acute. Arenes substituted with the electron withdrawing groups *p*-CO_2Me and *p*-CF_3 gave predominately HC products **10d** (48%) and **11d** (55%), with product distributions indicating cyclization favored the **CD** cation 40:60 and 26:74, respectively (Table 2, entries 4 and 5). Subsequent, trapping of the **CD** cation by the internal arene was presumably slowed by the electron withdrawing substituents, favoring halocyclization over FC closure (56:14 for R = CO_2Me, and 74:0 for R = CF_3).

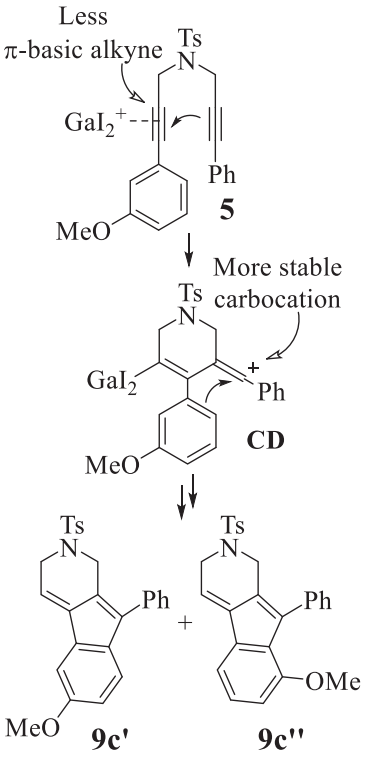
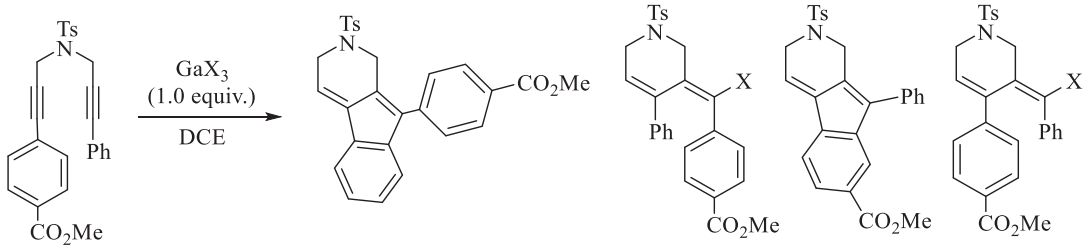


Figure 4

As expected from the observation that $GaCl_3$ gave higher yields of the FC cyclization product for symmetric diyne **1** (Scheme 1), changing the Ga(III) counterion also affected the chemoselectivity (FC:HC) of the products for unsymmetric diyne **6** (Table 3), though little apparent change in the overall regioselectivity (**AB**:**CD**) was observed (Table 3, column 4). While GaF_3 was unable to promote the reaction even at elevated temperatures (Table 3, entry 1), in all other cases the regioselectivity was found to be between 38:62 (Table 3, entry 2) and 30:70 (Table 3, entry 4), indicating the preferred reaction pathway proceeded through vinyl cation intermediate **CD**, though not overwhelmingly so (Figure 1). In the halide series Cl - Br - I, the ratio of HC product **10d** to FC product **10c** increased as the halide became more nucleophilic (Table 4, entries 2-4). For $GaCl_3$, the FC product **10c** was favored over the HC product **10d** (X = Cl) by 2:1 (Table 3, entry 2), whereas, for GaI_3 the HC product **10d** (X = I) was favored over the FC product **10c** by 4:1 (Table 3, entry 4). This is consistent with the proposed mechanism: as the nucleophilicity of the halide increases, its ability to compete with the *p*-methyl ester phenyl nucleophile in trapping the intermediate vinyl carbocation **CD** also increases, resulting in more halocyclization product **d** relative to **c**. In contrast, none of the halides were able to compete with the more nucleophilic phenyl, so vinyl halide **10b** was not observed in significant quantities and the amount of **10a** was essentially unchanged with the different gallium trihalides.

Table 3. Cyclizations of **6** with GaX_3



6 **10a** **10b** **10c** **10d**

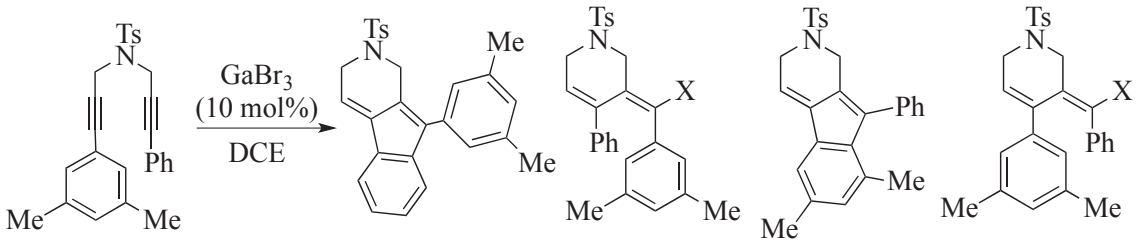
entry	GaX_3	(**a**:**b**:**c**:**d**)[a]	r.r. (**a**+**b**:**c**+**d**)	FC:HC (**c**:**d**)	major prod. (% yield)[b]
1[c]	GaF_3	0:0:0:0	NA	NA	NA
2	$GaCl_3$	38:0:42:20	38:62	42:20	**10c** (35)
3	$GaBr_3$	31:0:40:29	31:69	40:29	**10c** (29)
4	GaI_3	30:0:14:56	30:70	14:56	**10d** (48)
5[d]	$GaCl_3$	35:0:50:15	35:65	50:15	**10c** (41)
6[e]	GaI_3	24:8:4:64	32:68	4:64	**10d** (30)

[a]Product ratios determined from NMR integrations of crude reaction mixtures [b]Isolated yields of major products [c]80 °C, 48 h [d]0.6 equiv. $GaCl_3$ added over 48 h as 0.5 M solution in hexanes to a 0.05 M solution of diyne in DCE [e]1.5 equiv GaI_3, 0.4 M DCE

It was rationalized that the amount of **10d** could be further reduced, and the amount of **10c** maximized, by maintaining a low [Cl^-] through the slow addition of $GaCl_3$ to a more dilute solution of diyne. This proved marginally successful: when a solution of $GaCl_3$ was added to diyne **6** over a period of 48 h the apparent ratio of **10c**:**10d** was increased (4:1) relative to a single stoichiometric addition of catalyst (2:1), and **10c** could be isolated in 41% yield (Table 3, entry 5). Notably, 60 mol% of $GaCl_3$ was required for the full conversion of diyne **6**. This marks a significant increase from the 10 mol% successfully employed for the cycloisomerization of diyne **1** noted earlier (Scheme 1). The electron withdrawal of the *p*-CO_2Me substituent of **6** both slowed the reaction relative to **1** and favored the formation of HC product **10d**. Since production of vinyl chloride **10d** is a stoichiometric reaction with $GaCl_3$, the formation of **10d** slowly depletes the amount of catalyst. It was reasoned that the production of **10c** could be minimized with maximum yield of **10d** (X = I) using an excess GaI_3. However, treating diyne **6** with 1.5 equivalents of GaI_3 gave mixed results (Table 3, entry 6). While **10d** was increased relative to **10c** as expected (64:4), several new side-products were observed in significant quantities including a small amount of product consistent with **10b** (X = I). The HC product **10d** was only isolated in 30% yield.

The change in chemoselectivity seen for **6** was observed with electronically activated substrates as well. As noted above, treatment of dimethyl phenyl substituted diyne **4**, with stoichiometric GaI_3 gave a 15:34:51:0 mixture of products **8a**:**8b**:**8c**:**8d** (Table 2, entry 2). This ratio indicates the regioselectivity of the initial cyclization step was 49:51 (**AB**:**CD**). Treatment of **4** with 10 mol% of the less nucleophilic

$GaBr_3$ gave precisely the same ratio of products presumed to arise from each regioisomeric cation (49:51, **AB**:**CD**) (Scheme 2). However, the chemoselectivity was significantly altered, with GaI_3 favoring the HC product **8b** (X = I) over the FC product **8a** (34:15), and $GaBr_3$ favoring the FC product **8a** over the HC product **8b** (39:10).



4 **8a** **8b** **8c** **8d**

NMR ratio of products: 39 : 10 : 51 : 0

Scheme 2

In order to more directly compare the regiochemical outcomes of these cyclization conditions without the added complexity of the halocylization products, nosyl sulfonamide **12** was prepared and subjected to both GaI_3 and Bronsted acid catalyzed cyclization (Scheme 3). Electron donation from the *m*-methoxy (σ_{para} = -0.268)[13] and methyl (σ_{para} = -0.170)[13] substituents on the arenes of **12** were expected to activate both rings as nucleophiles such that the FC cyclization pathway would dominate over the HC pathway regardless of the regioselectivity of the initial cyclization (Figure 5). However, the alkynes of **12** possess an electronic difference. Donation from the methyl groups should increase the electron density of the adjacent alkyne (σ_{meta} = -0.069), while the *m*-methoxy substituted arene should decrease the electron density in the other alkyne (σ_{meta} = 0.115).[13] Based on the regiochemical outcomes of substrates in Table 2, the Bronsted acid conditions were expected to favor protonation of the more basic 3,5-dimethylphenyl substituted alkyne and give **13** as the major product via intermediate **B** (Scheme 3, left). Conversely, Ga(III) conditions were expected to favor the formation of the more stable carbocation **C** to give **14** and **15** as the major products (Scheme 3, right). Under TFA conditions, NMR of the crude reaction mixture indicated product **13** was favored 96:4 over products **14** and **15**, and **13** could be isolated in 75% yield (Scheme 3, left). As anticipated, under GaI_3 conditions no halocyclization products were observe, and the NMR indicated **14** and **15** were favored 6:4 over **13**. A mixture of the two FC products (2:1, **14**:**15**) was obtained in 60% yield (Scheme 3, right). Thus, the two different methods for catalyzing unsymmetric bisaryl diyne cyclization, Ga(III) Lewis acid and a strong Bronsted acid, resulted predictably in two different regioselectivities.

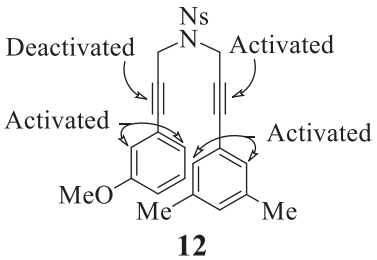


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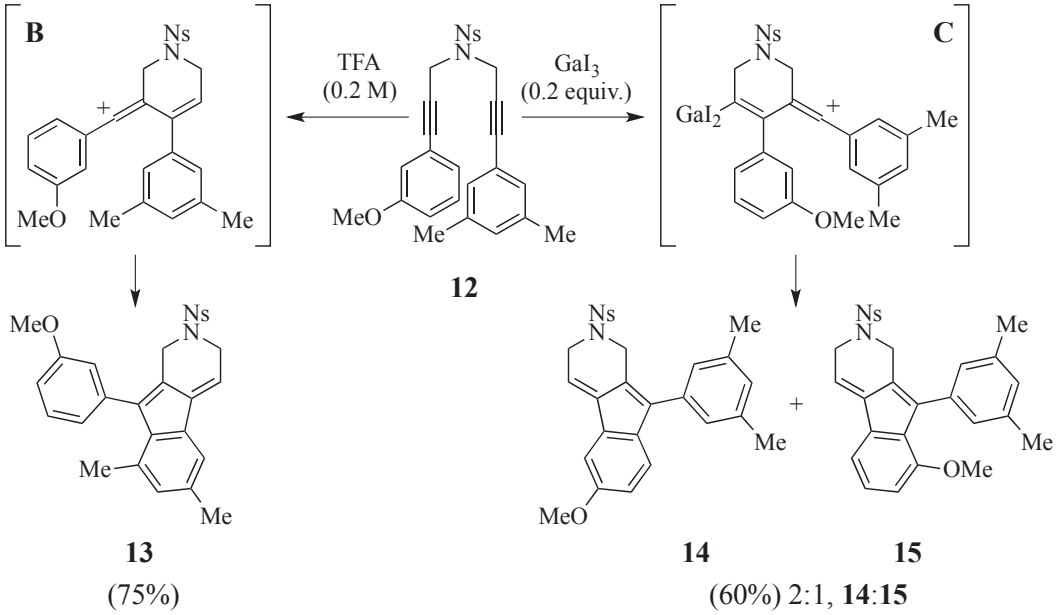
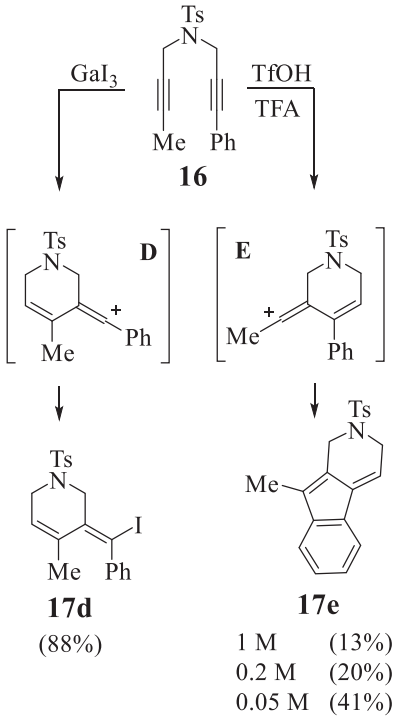
Figure 5



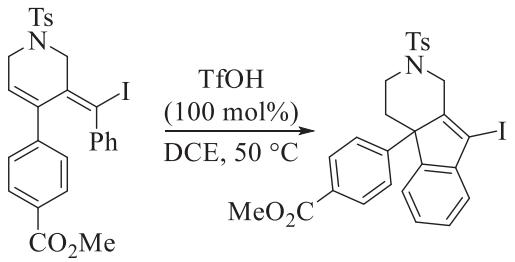
Scheme 3

The applicability of the Bronsted acid catalyzed cyclization to aryl/alkyl diynes was then investigated. As previously reported,[5] aryl/alkyl diyne **16** undergoes halocyclization in the presence of GaI_3 to give exclusively vinyl iodide **17d** (Scheme 4, left). The presumed intermediate of this reaction **D**, does not possess an arene nucleophile capable of intermolecular tapping of the cation. Success of the FC cyclization therefore requires the generation of the opposite regioisomer, carbocation **E** (Scheme 4, right). However, vinyl cation **E** is presumably higher in energy than the alternative vinyl cation **D**, which can be stabilized through resonance to the phenyl ring.

Under the TfOH/TFA conditions, **16** was converted to **17e** in only 20% isolated yield, with complete consumption of the starting material. Although uncharacterized, the mass balance of this reaction was consistent with the formation of highly conjugated polymers; broad, complex NMR peaks, and sparingly soluble bright yellow solids. These polymers can potentially be explained by the formation of unproductive carbocation **D**. As no obvious intramolecular pathway exists for this intermediate, intermolecular trapping of vinyl cation **D** by products and starting material of the ongoing reaction is likely to generate polymers. Consistent with this explanation, more concentrated reaction conditions (1 M) gave diminished yields of **17e** (13%) and more dilute reaction conditions (0.05 M) increased the yield to 41% (Scheme 4).



Scheme 4



10d **18** (44%)

Scheme 5

Finally, the applicability of bisaryl halocyclization product **10d** to further acid catalyzed cyclization previously observed for aryl/alkyl halocyclization products was assessed.[5] On treatment with TfOH, diyne **10d** gave the expected iodoindenopyridene **18** in 44% yield (Scheme 5). Angular aromatic groups have only rarely been observed in these tetrahydroindenopyridene ring systems.[13]

In conclusion, a versatile method to access both halocyclization and tandem cycloisomerization/Friedel-Crafts products from accessible *N*-tethered 1,6-diyne starting materials has been developed. Employing TfOH/TFA conditions, a strong preference for a single regioisomer arising from protonation of the more basic alkyne was observed. With GaX_3 conditions, a modest preference for products initiated at the less basic alkyne was observed. Dilute $GaCl_3$ favors the Friedel-Crafts cyclization products, and stoichiometric or super stoichiometric GaI_3 favors the halocyclization products. Bisaryl halocyclization products underwent further cyclization in the presence of strong acid to furnish tetrahydroindenopyridene scaffolds with a quaternary stereocenter from which an angular aromatic ring is appended. In addition, this chemistry has been shown to work efficiently with *N*-nosyl derivative **12**, which potentially enables facile deprotection[14] for further diversification of the amino nitrogen, a process now underway.

EXPERIMENTAL

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 117.42 kG (^{1}H 500 MHz, ^{13}C 125 MHz) at ambient temperature as noted. Hydrogen chemical shifts are expressed in parts per million (ppm) relative to the residual protio solvent resonance: $CDCl_3$ δ 7.26. For ^{13}C spectra, the centerline of the solvent signal was used as internal reference: $CDCl_3$ δ 77.00. Unless otherwise noted, each carbon resonance represents a single carbon (relative intensity). Flash chromatography was performed on silica gel-60 (43-60 μm). Commercially available anhydrous solvents were used as purchased.

Starting Materials. Diynes (1-8) were prepared in accordance with standard methods.[5] All other chemicals used in this study were purchased from commercial sources.

Typical experimental procedure for TfOH catalyzed cycloisomerization, diyne 6 to 10a. Diyne **6** (16.0 mg, 0.035 mmol) was added to a screw cap vial equipped with a stir bar and dissolved in TFA (0.1 M). Triflic acid was added (0.6 uL, 0.007 mmol), the vial was sealed and stirred for 1 h. The reaction was diluted with DCM (3 mL) and the organic layer washed with water (5 mL), followed by 0.5 M NaOH (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification via flash chromatography gave **10a** (pet ether:EtOAc, 4:1, Rf 0.45, 10.0 mg, 63%) as a bright yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 7.2

Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.25 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.17 (overlap, 1H), 6.69 (t, *J* = 4.1 Hz, 1H), 4.43 (s, 2H), 4.19 (d, *J* = 4.1 Hz, 2H), 3.98 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 143.7, 142.2, 138.7, 138.3, 136.4, 134.0, 133.6, 130.1 (2C), 129.6, 129.5 (2C), 128.5, 128.3 (2C), 128.1, 127.6 (2C), 125.4, 122.8, 119.9, 119.7, 52.3, 45.2, 43.7, 21.4. HRMS (ESI) *m/z* 458.1425 ([M+H]$^+$, 100%), calc'd for $C_{27}H_{24}NO_4S$ 458.1426.

Typical experimental procedure for GaI_3 catalyzed halocyclization of *N*-tosyl tethered 1,6-diynes, 7 to 11d. A single portion of GaI_3 (19.4 mg, 0.043 mmol) was added to an oven dried screw cap vial equipped with a stir bar and immediately sealed with a septum. The mass of GaI_3 was used to set the scale of the reaction. In a separate vessel, diyne **7** (20.1 mg, 0.042 mmol) was dissolved in DCE (0.2 M). This solution was added to the vial containing the GaI_3 via syringe, and the reaction allowed to stir at rt for 1 h. The reaction was diluted with DCM (4 mL) and the organic layer washed with 0.5 M NaOH (8 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification via flash chromatography gave **11d** (pet ether:EtOAc, 7:3, Rf 0.6, 13.8 mg, 55%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.82 – 6.72 (m, 5H), 6.54 (dd, *J* = 8.0, 1.5 Hz, 2H), 5.57 (t, *J* = 3.6 Hz, 1H), 4.46 (s, 2H), 4.13 (d, *J* = 3.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.4, 143.2 (q, $^5J_{C\text{-}F}$ = 1.4 Hz), 137.4, 135.5, 134.3, 129.90 (2C), 129.85 (2C), 128.6, 128.3 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 128.11, 128.05 (2C), 127.7 (2C), 127.2 (2C), 124.2 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 123.8 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 106.3, 56.6, 47.0, 21.5. HRMS (ESI) *m/z* 596.0378 ([M+H]$^+$, 100%), calc'd for $C_{26}H_{22}F_3INO_2S$ 596.0368.

TFA catalyzed cycloisomerization of *N*-nosyl tethered 1,6-diyne 12 to 13. Diyne **12** (14.2 mg, 0.029 mmol) was added to a screw cap vial equipped with a stir bar and dissolved in TFA (150 uL), and stirred for 2 h. The reaction was diluted with DCM (3 mL) and the organic layer washed with water (5 mL), followed by 0.5 M NaOH (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. ^{1}H NMR showed the crude isolate to be 97:2:1, **13**:**14**:**15**. Purification via flash chromatography gave **13** (pet ether:EtOAc, 4:1, Rf 0.55, 10.6 mg, 75%) as a bright yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.37 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.09 (s, 1H), 6.95 (ddd, *J* = 8.4, 2.6, 0.7 Hz, 1H), 6.80 (ddd, *J* = 7.5, 1.5, 0.7 Hz, 1H), 6.78 (s, 1H), 6.74 (dd, *J* = 2.6, 1.5 H, 1H), 6.50 (t, *J* = 4.1 Hz, 1H), 4.30 (s, 2H), 4.25 (d, *J* = 4.1 Hz, 2H), 3.85 (s, 3H), 2.30 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 149.9, 143.9, 139.8, 138.9, 137.7, 137.1, 135.3, 133.8, 132.3, 131.2, 129.6, 128.6 (2C), 126.5, 124.0 (2C), 120.7, 119.9, 118.4, 114.2, 113.2, 55.3, 45.2, 43.7, 21.1, 19.7. HRMS (ESI) *m/z* 489.1482 ([M+H]$^+$, 100%), calc'd for $C_{27}H_{25}N_2O_5S$ 489.1484.

GaI_3 catalyzed cycloisomerization of *N*-nosyl tethered 1,6-diyne 12 to 14 and 15. A single portion of GaI_3 (3.2 mg, 0.007 mmol) was added to an oven dried screw cap vial equipped with a stir bar and immediately sealed with a septum. The mass of GaI_3 was used to set the scale of the reaction. In a

separate vessel, diyne **12** (17.2 mg, 0.035 mmol) was dissolved in DCE (0.2 M). This solution was added to the vial containing the GaI_3 via syringe, and the reaction stirred at 60 °C for 2 h. The reaction was then diluted with DCM (4 mL) and the organic layer washed with 0.5 M NaOH (8 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. ^{1}H NMR showed the crude isolate to be 40:37:16, **13:14:15**. Purification via flash chromatography gave a mixture of **14** and **15** (pet ether:EtOAc, 4:1, R_f 0.55, 10.3 mg, 60%) as a bright yellow solid. Purification of this mixture via flash chromatography gave **14** ($CHCl_3$, Rf 0.6, 5 mg, 29%) and **15** ($CHCl_3$, Rf 0.75, 1 mg, 6%) as bright yellow solids. For **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.08 (s, 1H), 6.95 (s, 2H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.45 (t, *J* = 4.1 Hz, 1H), 4.60 (s, 2H), 4.35 (d, *J* = 4.1 Hz, 2H), 3.80 (s, 3H), 2.42 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 149.7, 144.2, 139.4, 138.7, 138.5 (2C), 135.2, 135.1, 133.1, 130.2, 128.6 (2C), 125.8 (2C), 124.1, 123.6 (2C), 120.8, 120.2, 112.7, 106.9, 55.7, 45.5, 44.4, 21.5 (2C). HRMS (ESI) *m/z* 489.1465 ($[M+H]^+$, 100%), calc'd for $C_{27}H_{25}N_2O_5S$ 489.1484. For **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.02 (s, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.90 (s, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.48 (t, *J* = 4.1 Hz, 1H), 4.50 (s, 2H), 4.34 (d, *J* = 4.1 Hz, 2H), 3.64 (s, 3H), 2.40 (s, 6H).

Cyclization of 10d to 18. Vinyl iodide **10d** (7.0 mg, 0.013 mmol) was added to a screw cap vial equipped with a stir bar and dissolved in DCE (0.1 M). Triflic acid was added (1 uL, 0.013 mmol), the vial was sealed, heated to 50 °C, and stirred for 3 h. The reaction was diluted with DCM (4 mL) and the organic layer washed with 0.5 M NaOH (8 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo.* Purification via flash chromatography gave **18** (pet ether:EtOAc, 4:1, Rf 0.40, 3.1 mg, 44%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.36 (br d, *J* = 7.6, 1H), 7.32 (ddd, *J* = 7.6, 7.4, 1.1 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.15 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.01 (br d, *J* = 7.4 Hz, 1H), 4.87 (dd, *J* = 12.9, 1.6 Hz, 1H), 3.86 (s, 3H), 3.84 (br d, *J* = 12.9 Hz, 1H), 3.28 (d, *J* = 12.9 Hz, 1H), 2.96 (br d, *J* = 14.0, 1H), 2.66 (ddd, *J* = 12.9, 12.7, 2.0 Hz, 1H), 2.37 (s, 3H), 1.54 (ddd, *J* = 14.0, 12.7, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 150.3, 149.1, 143.7, 143.5, 142.4, 134.2, 130.6 (2C), 129.7 (2C), 129.2, 127.8, 127.5 (2C), 127.3, 126.0 (2C), 123.7, 122.3, 95.9, 58.5, 52.2, 46.8, 42.5, 33.9, 21.5. HRMS (ESI) *m/z* ($[M+H]^+$, 100%) 586.0557, calc'd for $C_{27}H_{25}INO_4S$ 586.0549.

ACKNOWLEDGEMENTS

We thank the NIGMS CMLD initiative (P50 GM067041) for partial financial support, and the NSF for supporting the purchases of the NMR (CHE 0619339) and HRMS spectrometers (CHE 0443618). We also thank the NSF REU (CHE 1156666) for summer support for JAD, and the Boston University

Undergraduate Research Opportunities Program (UROP) for support for ACI.

REFERENCES

1. (a) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak, and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084.
2. (a) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317; (b) L. Zhang, J. Sun, and S. A. Kozmina, *Adv. Synth. Catal.*, 2006, **348**, 2271; (c) V. Michelet, P. Y. Toullec, and J.-P. Genêt, *Angew. Chem. Int. Ed.*, 2008, **47**, 4268.
3. For recent reports see: (a) A. L. Gibeau and J. K. Snyder, *Org. Lett.*, 2011, **13**, 16, 4280; (b) W. Rao, M. J. Koh, D. Li, H. Hirao, and P. W. H. Chan, *J. Am. Chem. Soc.*, 2013, **135**, 7926; (c) J. Schädlich, T. Lauterbach, M. Rudolph, F. Rominger, and A. S. K. Hashmi, *J. Organomet. Chem.*, 2015, **795**, 71.
4. (a) M. Yamaguchi and Y. Nishimura, *Chem. Commun.*, 2008, 35; (b) M. K. Gupta and T. P. O'Sullivan, *RSC Adv*., 2013, **3**, 25498; (c) C. Bour and V. Gandon, *Synlett*, 2015, **26**, 1427.
5. K. R. Strom, A. C. Impastato, K. J. Moy, A. J. Landreth, and J. K. Snyder, *Org. Lett.*, 2015, **17**, 2126.
6. For evidence of GaX_2^+ intermediacy see: (a) W. Henderson and M. J. Taylor, *lnorg. Chim. Acta*, 1998, **277**, 26; (b) S. Tang, J. Monot, A. El-Hellani, B. Michelet, R. Guillot, C. Bour, and V. Gandon, *Chem. Eur. J.*, 2012, **18**, 10239; (c) K. Surendra and E. J. Corey, *J. Am. Chem. Soc.*, 2014, **136**, 10918.
7. X. Huang, L. Zeng, Z. Zeng, and J. Wu, *Chem. Eur. J.*, 2011, **17**, 14907.
8. J. Barluenga, G. P. Romanelli, L. J. Alvarez-García, I. Llorente, J. M. González, E. García-Rodríguez, and S. García-Granda, *Angew. Chem. Int. Ed.*, 1998, **37**, 3136.
9. (a) K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii, and H. Ohno, *J. Org. Chem.*, 2011, **76**, 1212; (b) Y.-X. Zhang, L. Guo, Y.-H. Wang, L.-L. Zhu, and Z.-L. Chen, *Synth. React. Inorg. Met.-Org. Nano-Metal Chem.*, 2010, **40**, 241; (c) D. D. Vachhani, M. Galli, J. Jacobs, L. V. Meerveltb, and E. V. Van der Eycken, *Chem. Commun.*, 2013, **49**, 7171.
10. T. Xu, Q. Yang, W. Ye, Q. Jiang, Z. Xu, J. Chen, and Z. Yu, *Chem. Eur. J.*, 2011, **17**, 10547.
11. J.-J. Lian, P.-C. Chen, Y.-P. Lin, H.-C. Ting, and R.-S. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 11372.
12. J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Dover Publications, Inc., New York, 1963.
13. (a) D. Marshall, U.S. Patent 3,301,866, 1967; (b) J. Fruechtel, E. Dupont, T. Goebel, W. S. Schorderet, and J. Bouvier, Patent WO2,009,071,500, 2009.
14. T. Fukuyama, C. -K. Jow, and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.