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Synthesis of Halogenated Cyclic Enamines from Cyclic *N*-2-En-4-ynyl-*N*-1-ynylamides and *N*-Propargyl-*N*-1-ynylamides via a Tandem Iron Halide Promoted N-to-C Shift-Aza-Prins Cyclization Sequence

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Abstract: A facile and efficient N-to-C allyl shift-aza-Prins cyclization sequence of cyclic *N*-2-en-4-ynyl-*N*-1-ynylamides is promoted by iron(III) chloride, generating chloro-containing bridged bicyclic enamines in minutes and in high yields. This reaction involves an unprecedented formation of a ketenimine via Fe(III)-mediated N-to-C allyl rearrangement, followed by aza-Prins cyclization. This sequence can also be applied to the generation of brominated cyclobutenamine derivatives using Fe(III) bromide and *N*-propargyl-*N*-1-ynylamides.

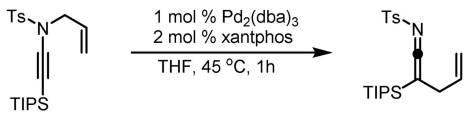
Keywords: Rearrangement; Cyclization; Halogenation

Ynamides are versatile and useful building blocks for the synthesis of biologically important molecules.[1] In the presence of activating reagents, ynamides deliver reactive keteniminium ion intermediates, which upon trapping with a tethered π-nucleophile at the α-position lead to nitrogen-containing cyclic compounds.[2] Alternatively, reactive ketenimines can be generated from ynamides by thermal aza-Claisen rearrangement of *N*-allyl ynamides[3] or palladium-catalyzed N-to-C allyl shift of *N*-allyl ynamides[4] or decarboxylative allyl rearrangement of *N*-alloc ynamides (Scheme 1).[5] These reactive ketenimines[6] can further be trapped by enamines intermolecularly to give amidines[4a–b] or a tethered olefin intramolecularly to afford cyclic imines.[4c–e] The key step of the palladium-catalyzed rearrangement of *N*-allyl ynamides starts with an oxidative addition of Pd(0) to the C–N bond to form an ynamido-Pd-π-allyl complex, which undergoes an N-to-C allyl migration followed by reductive elimination to form ketenimines.[3a] However, these palladium-catalyzed allylic migrations normally requires heating the reaction mixture up to 80 °C for 5–8 h.[4b] Moreover, in some cases, the transformations need additional phosphine ligands such as xantphos or BINAP.[4e] We envisioned that an easier route for N-to-C allyl shift of *N*-allyl ynamides would be to employ a simple Lewis acid. Here we report a facile synthesis of chlorinated bridged bicyclic enamines in stereoselective fashion via a novel iron(III) chloride promoted N-to-C allyl shift-aza-Prins cyclization sequence. Moreover, this strategy can be applied to the synthesis of brominated cyclobutenamine derivatives from *N*-propargyl-*N*-1-ynylamides and iron (III) bromide.

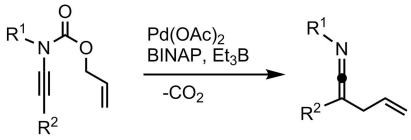
The synthesis of the parent six-membered ring *N*-2-en-4-ynyl-*N*-1-ynylamide **1a** was achieved starting from cyclohexane-1,3-dione using the known procedures (see Supporting Information for details). First, a screen of Lewis acids was undertaken, while CH_2Cl_2 was employed as the solvent under an atmosphere of N_2 (Table 1). Upon treatment with 1.1 equiv. of $FeCl_3$ at rt for 1 min, **1a** was transformed into the chlorine-containing bicyclo[3.2.1]octenamine **2a** in 40% yield (Table 1, entry 1). The structure and relative stereochemistry of **2a** were confirmed by X-ray diffraction analysis.[7] Upon increasing the loading of $FeCl_3$ from 1.1 to 1.5 equiv., the yield of **1a** increased from 40 to 65% (Table 1, entry 2). Pleasingly, the yield of **2a** could be considerably improved to 83% when the reaction temperature was lowered to 0 °C (Table 1, entry 3). The reaction completed in 5 min at −10 °C. However, the yield of **2a** did not increase (Table 1, entry 4). The use of $FeCl_3$ in several solvents such as

Previous work:

(a) Palladium-catalyzed N-to-C allyl shift of *N*-allyl ynamides (Hsung's group[4])

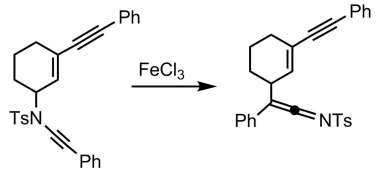


(b) Palladium-catalyzed decarboxylative allyl rearrangement of *N*-alloc ynamides (Cook's group[5])



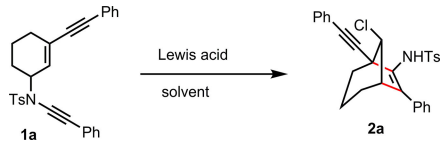
This work:

Iron halide promoted N-to-C shift of cyclic *N*-2-en-4-ynyl-*N*-1-ynylamides



Scheme 1. Synthesis of ketenimines from ynamides

Table 1. Optimization of the Iron-Promoted Chlorinated Bridged Bicyclic Enamines Formation.



entry	Lewis acid	equiv.	solvent	*t* (°C)	time	yield (%)[a]
1	$FeCl_3$	1.1	CH_2Cl_2	26	1 min	40
2	$FeCl_3$	1.5	CH_2Cl_2	27	1 min	65
3	$FeCl_3$	1.5	CH_2Cl_2	0	1 min	83
4	$FeCl_3$	1.5	CH_2Cl_2	−10	5 min	75
5	$FeCl_3$	1.5	toluene	25	3 min	16
6	$FeCl_3$	1.5	THF	30	12 h	–[b]
7	$FeCl_3$	1.5	ether	24	20 min	–[b]
8	$AlCl_3$	1.5	CH_2Cl_2	24	5 min	26
9	$FeBr_3$	1.5	CH_2Cl_2	0	1 min	16[c]
10	$FeCl_2$	1.5	THF	40	12 h	–[b]
11	$InCl_3$	1.5	CH_2Cl_2	24	1 min	–[b]
12	TMSCl	1.5	CH_2Cl_2	30	15 h	–[d]
13	$ZnCl_2$	1.5	CH_2Cl_2	30	2 h	–[b]

[a] Isolated yields from column chromatography over silica gel.
[b] Not detected.
[c] The corresponding bromide was isolated.
[d] **1a** was recovered quantitatively.

toluene, THF or ether did not result in better yields (Table 1, entries 5–7).

Other Lewis acids, for example, $AlCl_3$, $FeBr_3$, $FeCl_2$, TMSCl, and $InCl_3$ were also screened. Among them, only $AlCl_3$ and $FeBr_3$ gave low conversions to the cyclized product **2a** and the corresponding brominated bridged bicyclic enamine, respectively (Table 1, entries 8 and 9). In the presence of $FeCl_2$ and $InCl_3$, **1a** underwent decomposition (Table 1, entries 10 and 11). Treatment of **1a** with TMSCl in CH_2Cl_2 resulted in recovery of the starting substrate (Table 1, entry 12). Subjection of **1a** to $ZnCl_2$ (1.5 equiv.) in CH_2Cl_2 at r.t. for 2 h gave a mixture of unidentified compounds (Table 1, entry 13). Moreover, when the five-membered ring analogue **3a** was treated with 6 M aq HCl (9 equiv.), a mixture of the *E* and *Z* isomers of the corresponding α-chloro enamides was isolated.[8] Therefore, the use of 1.5 equiv. of $FeCl_3$ in CH_2Cl_2 at 0 °C is considered to be the optimal reaction conditions for the transformation of **1a** to **2a** (Table 1, entry 3).

With optimum reaction conditions established, the scope of the $FeCl_3$-promoted N-to-C allyl shift-aza-Prins cyclization sequence was explored. Table 2 summarized the results that were obtained with a variety of cyclic *N*-2-en-4-ynyl-*N*-1-ynylamides. The scope with respect to the substitution on the ynamide fragment was first investigated. Ynamides **1a–e**, bearing an electron-neutral aryl group on the ynamide terminus, smoothly delivered the corresponding products **2a–e** in good yields (71–83%, Table 2, entries 1–5). Substrate **1f**, featuring a fluorine atom on the phenyl ring, was unaffected and delivered the desired product **2f** in 74% yield (Table 1, entry 6). Other halogen substituents like Cl (**1g**) and Br (**1h**) were less efficient and afforded the corresponding products **2g** and **2h** in 45 and 44% yield, respectively (Table 2, entries 7–8). Adding an electron-withdrawing ester group to the phenyl group, **1i**, gave the expected product **2i** in 54% yield (Table 2, entry 9), whereas placing an electron-donating methoxy group at C4 of the phenyl ring, **1j**, (Table 2, entry 10) failed to deliver any cyclized product. When 3-thienyl-substituted ynamide **1k** was treated with $FeCl_3$ (Table 2, entry 11), a 49% yield of the desired product **2k** was achieved. Alkyl substituents at the ynamide terminus, **1l–o**, were suited for the transformation, furnishing the corresponding chlorinated bicyclic enamines **2l–o** in good yields (65–82%, Table 2, entries 12–15). The influence of the substituent (R^2) at the alkyne fragment was next surveyed while keeping the phenyl group at the ynamide terminus fixed. As can be seen from Table 2, entries 16–18, both aryl (**1p**, **1q**) and alkyl (**1r**) substituents at the alkyne terminus are efficient and produced the expected chlorinated bridged bicyclic enamines (**2p**[7]–**r**) in high yields (73–82%). Moreover,

five-membered ring substrates **3a–e** (Table 2, entries 19–23) also underwent the N-to-C allyl shift-aza-Prins cyclization effectively to give the corresponding bicyclic enamines **4a–e** in good yields (54–75%).

Table 2. Substrate Scope.

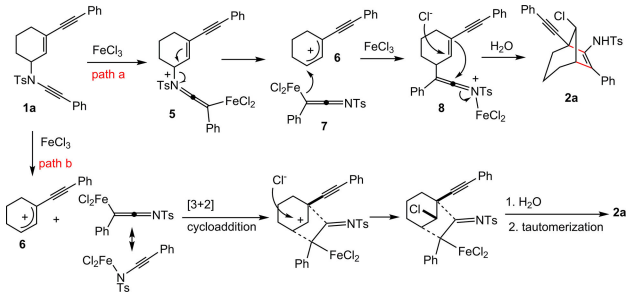
1, n = 2
3, n = 1

2, n = 2
4, n = 1

entry	substrate	n	R^1	R^2	product	yield (%)[a]
1	**1a**	2	Ph	Ph	**2a**[b]	83
2	**1b**	2	3-MeC_6H_4	Ph	**2b**	82
3	**1c**	2	4-MeC_6H_4	Ph	**2c**	71
4	**1d**	2	4-PhC_6H_4	Ph	**2d**	75
5	**1e**	2	naphth	Ph	**2e**	76
6	**1f**	2	4-FC_6H_4	Ph	**2f**	74
7	**1g**	2	4-ClC_6H_4	Ph	**2g**	45
8	**1h**	2	4-BrC_6H_4	Ph	**2h**	44
9	**1i**	2	3-$CO_2MeC_6H_4$	Ph	**2i**	54
10	**1j**	2	4-$OMeC_6H_4$	Ph	**2j**	–[c]
11	**1k**	2	3-thienyl	Ph	**2k**	49
12	**1l**	2	*n*-hexyl	Ph	**2l**	82
13	**1m**	2	3-Cl-propyl	Ph	**2m**	82
14	**1n**	2	*n*-hexyl	4-ClC_6H_4	**2n**	77
15	**1o**	2	*n*-hexyl	3-$CO_2EtC_6H_4$	**2o**	65
16	**1p**	2	Ph	3-$CO_2EtC_6H_4$	**2p**[b]	82
17	**1q**	2	Ph	4-ClC_6H_4	**2q**	73
18	**1r**	2	Ph	*n*-hexyl	**2r**	73
19	**3a**	1	Ph	Ph	**4a**	64
20	**3b**	1	4-MeC_6H_4	Ph	**4b**	57
21	**3c**	1	4-ClC_6H_4	Ph	**4c**	54
22	**3d**	1	*n*-hexyl	Ph	**4d**	65
23	**3e**	1	3-Cl-propyl	Ph	**4e**[b]	75

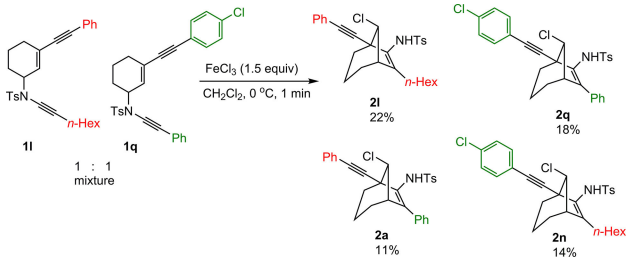
[a] Isolated yields from column chromatography over silica gel.
[b] The structure was confirmed by X-ray diffraction analysis.
[c] Not detected.

A postulated mechanism for the transformation of cyclic *N*-2-en-4-ynyl-*N*-1-ynylamide **1a** to chlorinated bridged bicyclic enamine **2a** is outlined in Scheme 2. Activation of the ynamide moiety in **1a** by $FeCl_3$ leads to keteniminium ion **5** (path a). Subsequently, detachment of the iron-ketenimine moiety generates the stable allylic carbonium ion **6**. Re-addition of the iron-ketenimine **7** at the allylic carbon followed by activation of the resulting ketenimine with iron chloride gives intermediate **8**, which undergoes an aza-Prins cyclization[9] to furnish the chlorinated bridged bicyclic enamine **2a**. However, an alternative mechanism can also be considered (path b). Complexation of $FeCl_3$ to the NTs group may cause the detachment of iron-complexed ynamide/ketenimine from the cyclohexene ring to give allylic carbonium ion **6**. A formal [3+2] cycloaddition between the allylic cation and the double bond of the ketenimine together with trapping of the resulting secondary carbocation by a chloride ion affords an imine intermediate, which after hydrolysis and tautomerization furnishes **2a** (path b). Miller reported the formation of 8-chlorobicyclo[3.2.1]oct-6-ene derivatives by zinc chloride catalyzed [3+2] cycloaddition of cyclic allylic chlorides to alkynes.[10] It must be noted that the stabilization by the conjugated π systems of the phenylalkyne at C3 of the six-membered ring was critical since the substrate with a simple methyl group at C3 did not undergo the N-to-C allyl shift reaction path.[11]



Scheme 2. Proposed Mechanism for the Formation of **2a** from **1a**

To further prove the proposed intermolecular N-to-C allyl shift, a crossover experiment in which an equimolar mixture of ynamides **1l** and **1q** was subjected to the optimal reaction conditions and the ratio of the products was examined by NMR spectroscopy (Scheme 3). The analysis of the spectra clearly indicates that four possible products **2l** (22%) and **2q** (18%), **2a** (11%), and **2m** (14%) were obtained. This result consists with an intermolecular allyl transfer

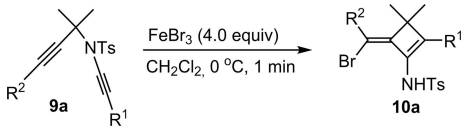


Scheme 3. Crossover Experiment

process, which involves a detachment-re-addition sequence of iron-ketenimine moiety **7** to the allylic carbon center depicted in path a, Scheme 2.

The synthesis of brominated cyclobut-1-en-1-amine derivatives from *N*-propargyl-*N*-1-ynylamides can also be demonstrated using the same approach.[12] The *N*-propargyl-*N*-1-ynylamides **9a** was easily prepared starting from commercially available 2-methyl-3-butyn-2-amine (see Supporting Information for details). First, **9a** was subjected to various reaction parameters (Lewis acid, solvent, and temperature). The survey revealed that treatment of **9a** with 4.0 equiv. of $FeBr_3$ in CH_2Cl_2 at 0 °C under an atmosphere of nitrogen for 1 min gave the best result (See Supporting Information for details). Thus, under this optimum reaction conditions, a major product, identified as the brominated cyclobut-1-en-1-amine **10a**, was obtained in 68% yield (Table 3, entry 1). The structure of **10a**, possessing the *Z*-configuration at the exocyclic olefin, was determined with ^{1}H NMR measurements and further confirmed by X-ray crystallography.[7] With the optimal reaction conditions in hand, the scope of this transformation with respect to substitutions of both ynamide and alkyne termini was explored. Results of the formation of brominated cyclobut-1-en-1-amine derivatives from *N*-propargyl-*N*-1-ynylamides are shown in Table 3. In general, electron-neutral aryls on both ynamide and alkyne termini were accommodated, affording the desired products **10a–e** in good yields (51–68%, Table 3, entries 1–5). The halogen-containing substrates, **9f–k**, were also tolerated, generating the anticipated brominated cyclic enamines **10f–k** in 46–83% isolated yields (Table 3, entries 6–11). However, a lower yield of **10l** was obtained in the reaction of **9l**, which is substituted with an electron-withdrawing ester group at C3 of the phenyl group on the ynamide terminus (37%, Table 3, entry 12). The low yield was also found with substrate **9m** bearing an electron-donating methoxy group at C3 of the phenyl ring on the ynamide terminus (33%, Table 1, entry 13). Unfortunately, running the reaction with substrates bearing a methoxy group at C2 or C4 of the phenyl ring on the ynamide moiety led to complete decomposition upon treatment with $FeBr_3$ (Table 3, entries 14–15). Moreover, substrates with an alkyl substitution at the ynamide terminus, **9p** and **9q**, were also reactive, providing the desired compounds **10p** and **10q**, albeit with diminished yields (33–40%, Table 3, entries 16–17).

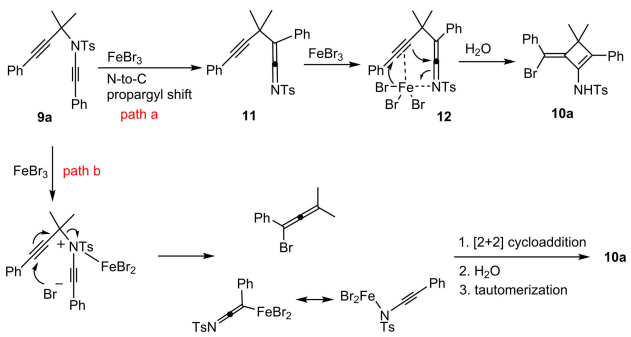
Table 3. Substrate Scope.



entry	substrate	R^1	R^2	product	yield (%)[a]
1	**9a**	Ph	Ph	**10a**[b]	68
2	**9b**	2-MeC_6H_4	Ph	**10b**[b]	55
3	**9c**	4-MeC_6H_4	Ph	**10c**	51
4	**9d**	Ph	2-MeC_6H_4	**10d**	65
5	**9e**	2-MeC_6H_4	2-MeC_6H_4	**10e**[b]	57
6	**9f**	2-BrC_6H_4	Ph	**10f**	57
7	**9g**	4-ClC_6H_4	Ph	**10g**	75
8	**9h**	2-BrC_6H_4	2-MeC_6H_4	**10h**	60
9	**9i**	Ph	4-ClC_6H_4	**10i**	46
10	**9j**	2-MeC_6H_4	4-ClC_6H_4	**10j**	60
11	**9k**	4-ClC_6H_4	4-ClC_6H_4	**10k**	83
12	**9l**	3-$CO_2MeC_6H_4$	Ph	**10l**	37
13	**9m**	3-$OMeC_6H_4$	Ph	**10m**	33
14	**9n**	2-$OMeC_6H_4$	Ph	**10n**	–[c]
15	**9o**	4-$OMeC_6H_4$	Ph	**10o**	–[c]
16	**9p**	*n*-hexyl	Ph	**10p**	33
17	**9q**	3-Cl-propyl	Ph	**10q**	40

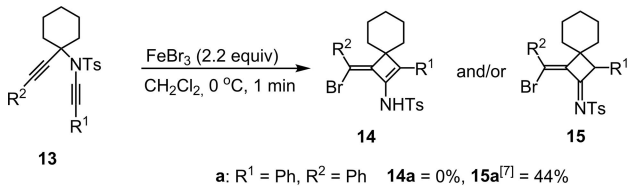
[a] Isolated yields from column chromatography over silica gel.
[b] The structure was confirmed by X-ray diffraction analysis.
[c] Not detected.

A formal alkyne aza-Prins cyclization reaction path[13] is suggested for the formation of cyclobutenamine **10a** (Scheme 4). An N-to-C propargyl shift of **9a** with $FeBr_3$ leads to ketenimine **11**. Coordination of the iron center to both the alkyne and the nitrogen atom provides intermediate **12**, which enables a *syn*-carbobromination of the alkyne, furnishing cyclobut-1-en-1-amine[14] **10a** possessing the *Z*-configuration at the newly formed exocyclic olefin after aqueous work-up. It must be mentioned that Fe(III) halides are known to promote alkynes aza-Prins-type cyclization.[9a] Alternatively, an iron bromide assisted S_N2' type attack of a bromide on the phenylacetylene affords a bromoallene and an iron-complexed ynamide/ketenimine. A formal [2+2] cycloaddition of the allene with the ketenimine gives an imine, which then undergoes hydrolysis and tautomerization to generate **10a** (path b, Scheme 4).[15]



Scheme 4. Proposed Mechanism for the Formation of **10a** from **9a**

Six-membered ring *N*-propargyl-*N*-1-ynylamides **13** also reacts with $FeBr_3$ under the same reaction conditions to produce spiro compounds **14** and **15** (Scheme 5). Thus, treatment of **13a** with 2.2 equiv. of $FeBr_3$ at 0 °C in CH_2Cl_2 for 1 min gave a 44% yield of spiro imine[16] **15a**,[7] which was formed after an *endo* to *exo* double-bond migration of the initial formed spiro enamine **14a**. Moreover, while compounds **13b–d** gave only spiro enamines **14b**[7]**–d** (51–75%), substrate **13e** afforded both spiro-enamine **14e**[7] and -imine **15e** in 40 and 33% yield, respectively.



a: R^1 = Ph, R^2 = Ph **14a** = 0%, **15a**[7] = 44%
b: R^1 = 2-MeC_6H_4, R^2 = Ph **14b**[7] = 75%, **15b** = 0%
c: R^1 = 1-Naph, R^2 = Ph **14c** = 51%, **15c** = 0%
d: R^1 = Ph, R^2 = 4-PhC_6H_4 **14d** = 58%, **15d** = 0%
e: R^1 =4-ClC_6H_4, R^2 = Ph **14e**[7] = 40%, **15e** = 33%

Scheme 5. Synthesis of **14** and **15**

In conclusion, we have developed a new approach of N-to-C shift-aza-Prins cyclization tandem process from cyclic *N*-2-en-4-ynyl-*N*-1-ynylamides and *N*-propargyl-*N*-1-ynylamides. The reactions convert a wide range of π-tethered ynamides to halogenated cyclic enamines with iron(III) halides. This method is advantageous as it employs inexpensive iron halides under mild reaction conditions in short reaction times and in good to high yields.

Experimental Section

Synthesis of *N*-((1*R**,5*R**,8*R**)-8-Chloro-7-phenyl-5-(phenylethynyl)bicyclo[3.2.1]oct-6-en-6-yl)-4-methyl-benzenesulfonamide (2a)

To a fire-dried 2-neck-round flask with a stir bar were added $FeCl_3$ (0.06 g, 0.375 mmol, 1.5 equiv.) and CH_2Cl_2 (20.0 mL); the mixture was then cooled to 0 °C. A solution of **1a** (0.11 g 0.250 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) was added to the mixture. After complete consumption of the starting material (TLC, 1 min), the reaction mixture was quenched with NEt_3 (3.0 mL). The resulting mixture was filtered thought a pad of Celite/silica gel/Celite and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, ethyl acetate/hexanes 1:10) gave **2a** as a white solid; yield: 0.10 g (0.208 mmol. 83%).

Synthesis of (*Z*)-*N*-(4-(Bromo(phenyl)methylene)-3,3-dimethyl-2-phenylcyclobut-1-en-1-yl)-4-methylbenzenesulfonamide (10a)

To a flame-dried 2-neck-round flask with a stir bar were added $FeBr_3$ (0.33 g, 1.00 mmol) and CH_2Cl_2 (4.0 mL). The mixture was cooled to 0 °C. Ynamide **9a** (0.10 g, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with NEt_3 (5.0 mL). The resulting mixture was filtered thought a pad of Celite/silica gel/Celite and concentrated under reduced pressure. Purification of the residue by flash column chromatography (ethyl acetate/hexanes 1:20) gave compound **10a** as a white solid; yield: 0.08 g (0.17 mmol, 68%).

Supporting Information

Spectroscopic characterization and copies of $^1H/^{13}C$ NMR spectra of compounds **1a–r**, **2a–r**, **3a–e**, **4a–e**, **9a–q**, **10a–q**, **13a–e**, **14b–e**, **15a**, **15e** and X-ray crystallographic information files for compounds **2a**, **2p**, **4e**, **10a**, **10b**, **10e**, **14b**, **14e** and **15a** are available as supporting information.

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