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Heavier Alkaline Earth Catalyzed Ene-yne Cyclizations: Atom-Efficient Access to Tetrahydroisoquinoline Frameworks

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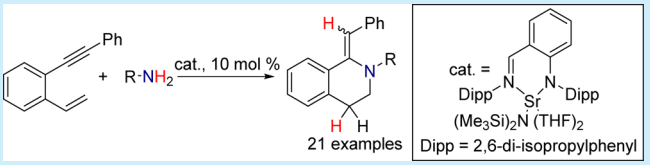
Supporting Information

ABSTRACT: Tetrahydroisoquinoline frameworks may be accessed with 100% atom efficiency through the alkaline earth catalyzed addition of primary amines to ene-yne substrates through a sequence of intermolecular alkene and intramolecular alkyne hydroamination steps.

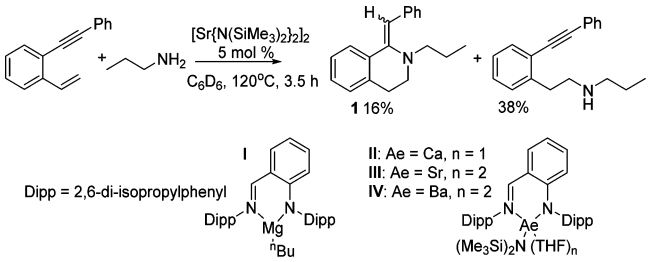


Tetrahydroisoquinoline (THIQ) ring systems are constituents of a wide range of alkaloids and synthetic organic and pharmaceutical compounds.[1] Methods for their preparation have, therefore, become increasingly desirable over the past few decades.[2] The Bischler−Napieralksi, Pictet−Spengler, and Pomeranz−Fritsch reactions are among the most long-standing synthetic methods for the preparation of isoquinoline derivatives.[3] Other methods include intramolecular oxetane ring openings,[4] multicatalytic three component coupling reactions with gold complexes,[5] oxetane directed aza-Diels−Alder reactions of indoles,[6] and reductive amination/aza-Michael sequences.[7] The development of enantioselective, catalytic acyl-Pictet−Spengler reactions[8] has also been achieved as well as calcium-catalyzed Pictet−Spengler reactions.[9] Their utility notwithstanding, each of these systems requires multistep protocols and/or initial condensation reactions to provide the necessary imine intermediates, and catalytic routes to 1-benzyltetrahydroisoquinolines, such as the alkaloids coclaurine and roefractine,[10,11] are scarce. In this contribution we describe a route to THIQ derivatives, which proceeds with absolute atom economy. This process is mediated by a sequence of heavier alkaline earth-catalyzed intermolecular alkene and intramolecular alkyne hydroamination steps to afford exocyclic enamine THIQ frameworks, which are primed for further reaction.[12]

We have previously reported that the intermolecular hydroamination of vinylarenes, 1,3-dienes, and alkynes may be achieved with a broad scope of amines including primary, secondary, and *N*-heterocyclic amines through the action of group 2-based catalysts.[13] The hydroamination of alkynes is generally viewed as being more facile than that of alkenes because of the higher reactivity and electron density of C≡C bonds,[14] while the more entropically demanding intermolecular hydroamination of alkenes is less developed than its intramolecular variant.[15] We, thus, speculated that sequences of kinetically distinct reaction steps could be incorporated into syntheses, which exploit the potential for multiple C−N bond forming processes encapsulated in a single ene-yne substrate.

An initial NMR scale reaction between 1-phenyl-2-(*o*-styrenyl)ethyne and *n*-propylamine in C_6D_6 in conjunction with $[Sr\{N(SiMe_3)_2\}_2]$ was undertaken (Scheme 1) employing

Scheme 1



the 40:20:1 ratio of substrate/amine/catalyst utilized by Marks for divinylbenzene hydroamination.[16] Whereas heating for an initial period of 14 h at 90 °C provided only 37% conversion to {2-[*o*-(2-phenylethynyl)phenyl]ethyl}-propylamine, an increase of the reaction temperature to 120 °C for a further 3.5 h provided 16% of the product of intramolecular ring closure, the desired THIQ product, 1-methylene-3,4-dihydro-2*H*-isoquinoline (**1**), along with further intermolecular alkene hydroamination (38%) (Scheme 1). Counter to expectation, these observations inferred that intermolecular hydroamination proceeded chemoselectively at the alkene moiety rather than the more sterically hindered but electronically activated acetylene substituent. A reaction performed under identical conditions but with a $[Ca\{N(SiMe_3)_2\}_2]$ precatalyst did not result in any viable yield of the cyclized product.

These encouraging observations prompted further development of the precatalyst through use of the heteroleptic anilido-imine supported alkaline earth reagents (**I**−**IV**, Scheme 1), which have been reported by Sarazin and co-workers[17] to

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provide superior hydroamination activity over the homoleptic metal bis(trimethylsilyl)amides.[18] Compounds **I**–**IV** were found to be effective catalysts for the intermolecular hydroamination of the styrene unit followed by alkyne cyclohydroamination with *n*-propylamine to afford 1-methylene-3,4-dihydro-2*H*-isoquinoline (**1**) in good to excellent yields using a moderately low catalyst loading of 10 mol % (Table 1).

Table 1. Hydroamination of 1-Phenyl-2-(*o*-styrenyl)ethyne with *n*-Propylamine Catalyzed by I–IV[a]

entry	cat.	loading (mol %)	time (h)	conversion **1**/X/amine (%)[b]
1	**I**	10	12	6:4:90
2[c]	**I**	10	43	23:12:65
3	**II**	5	16	32:68
4	**III**	5	16	43:57
5	**II**	10	15	71:29
6	**III**	10	14	99
7	**IV**	10	12	99

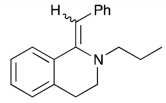
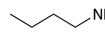
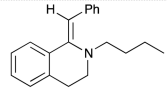
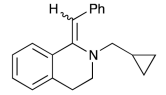
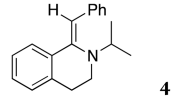
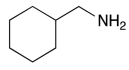
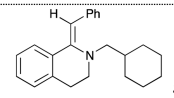
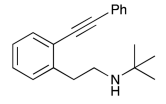
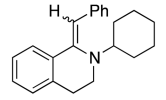
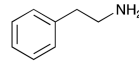
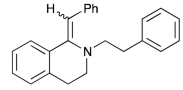
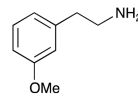
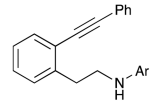
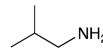
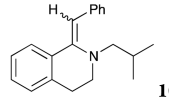
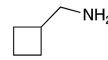
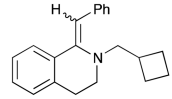
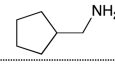
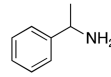
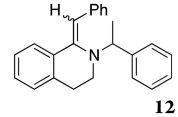
[a]Substrate:amine = 2:1, 5–10 mol % of catalyst, C_6D_6, [amine] = 0.33 M, 130 °C. [b]Monitored by ^{1}H NMR. Conversion based on ratio of THIQ product/intermediate/unreacted amine. [c]Temperature 140 °C.

Consistent with the previous reports of Sarazin and coworkers, the catalytic activity was observed to increase with increasing atomic weight of the group 2 element employed. These effects are rationalized by extra rigidity encountered within the iminoanilide ligand framework in comparison to previously studied β-diketiminate ligands.[15] The Mg precatalyst **I** displayed the lowest activity and was ineffective for the cyclization of the *N*-propylphenethylamine intermediate (entries 1 and 2). Although the Ba precatalyst **IV** provided the highest activity (entry 7), the Sr complex **III** provided quantitative conversion to the exocyclic enamine THIQ product after 14 h at 130 °C (entry 6). With its combination of acceptably high activity and greater ease of precatalyst synthesis, the strontium species **III** was, thus, selected for further study.

The scope of the hydroamination of 1-phenyl-2-(*o*-styrenyl)-ethyne catalyzed by **III** was examined with a range of commercially available primary alkyl amines (Table 2). Although cyclization could be achieved using 5 mol % of **III**, use of 10 mol % of the precatalyst provided significantly increased conversions. In all cases, regioselective styrene hydroamination to provide the *anti*-Markovnikov product was observed to have occurred first followed by insertion of the alkyne into the resulting Sr–N bond. The fastest rate of catalysis was achieved with *n*-propyl amine, which provided quantitative conversion to **1** in under 15 h (entry 1). Products formed from amines containing bulky substituents near the C–NH_2 moiety were generally formed in lower yields than *N*-methylene substituted amines. Good yields with the more bulky amines could be obtained, however, if the temperature was increased from 130 to 140 °C (entries 5–6, 9, 11–12), allowing purification and characterization of the otherwise hydrolytically sensitive products in their reduced form ($NaBH_4$, compounds **22**–**37**, Supporting Information).

Whereas cyclopropylmethylamine was successfully cyclized (entry 3), the cyclopentyl-substituted methylamine displayed no evidence for the formation of the alkene hydroamination-phenethylamine product (entry 13), even under more forcing conditions over 6 days, while the intermediate cyclobutylmethylamine provided only moderate conversion (entry 12).

Table 2. Hydroamination of 1-Phenyl-2-(*o*-styrenyl)ethyne with Primary Alkyl Amines Catalyzed by III[a]

entry	amine	product	time/conversion[b] (h/%)	*E*/*Z* ratio[b]
1		 **1**	15/99	3:1
2		 **2**	15/24 22[c]/99	- -
3		 **3**	15/97	2:1
4[d]		-	15/0	-
5		 **4**	15/57 17[c]/64 4[e]/73	- - -
6		 **5**	12.5[c]/38 4[e]/73	- -
7		 **6**	15/<3	-
8		 **7**	15/25	1:2.6
9[c]		 **8**	13/56 12.5/65 24/70	1.1:1 1:1.6 1:2.6
10[c]		 **9**	12.5/10	-
11		 **10**	15/64	4.4:1
12		 **11**	12.5/26 13[c]/36	1:0.28 1:1.2
13[d]		-	12.5/0	-
14		 **12**	13/20 74[e]/69	1:2.5 1:2.5

[a]Reaction conditions: [cat]/[amine]/[substrate] = 1:10:20 in C_6D_6 at 130 °C, [amine] = 0.33 M, catalyst = **III**. [b]Determined by ^{1}H NMR spectroscopy. [c]Temperature 140 °C. [d]No conversion of amine to intermolecular addition intermediate product nor subsequent cyclization. [e]Extra 5 mol % of catalyst added and heated further for the time specified.

Presumably, the rate of cyclization of cycloalkanemethylamines depends on a balance between steric factors, ring strain, and

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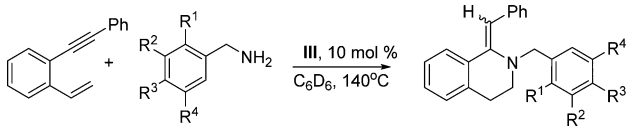
Table 3. Hydroamination of 1-Phenyl-2-(*o*-styrenyl)ethyne with Substituted Benzyl Amines Catalyzed by III[a]



entry	R^1	R^2	R^3	R^4	time (h)	conversion (%)[b]	E/Z[b]
1	H	H	H	H	12.5, 29	99(**13**), 99(**13**)	1.2:1, 1:2
2[c]	H	H	OMe	H	10, 15	68(**14**), 72(**14**)	1:1.1, 1:1.8
3	H	H	O^{t}Bu	H	13, 28, 12[c]	55(**15**), 63(**15**), 85(**15**)	1:0.9, 1:2, 1:2
4	H	OMe	OMe	H	12.5[d]		
5	H	OMe	H	OMe	15, 32	77(**16**), 85(**16**)	1:1.3, 1:2.6
6	H	OMe	H	H	12.5, 27	83(**17**), 90(**17**)	1:0.67, 1:1.3
7	OMe	H	H	OMe	10, 15	80(**18**), 82(**18**)	1:1, 1:1.5

[a]Reaction conditions: [cat]/[amine]/[substrate] = 1:10:20 in C_6D_6 at 140 °C, [amine] = 0.33 M. [b]Determined by ^{1}H NMR spectroscopy. Compound number in parentheses. [c]Extra 5 mol % of catalyst added and heated further for amount of time specified. [d]No conversion of amine to intermolecular addition intermediate product nor subsequent cyclization.

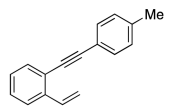
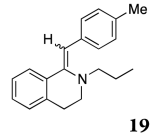
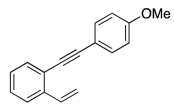
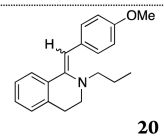
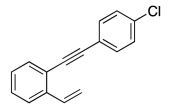
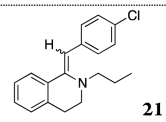
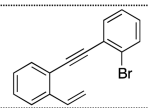
destabilizing effects encountered within the ring to allow a favorable conformation in the THIQ framework. The *E*:*Z* product ratio was also affected by the steric demands of the amine substrate with more sterically encumbered amines providing the *Z* isomer as the major product. In the case of 3-methoxyphenethylamine (entry 10) cyclization was unsuccessful. During the course of heating at 140 °C over 5 days, this reaction was accompanied by double hydroamination of the secondary amine intermediate. For reactions with methylbenzylamine (Table 2, entry 14) and benzyl amine (Table 3, entry 1) 15 mol % of catalyst was required to achieve a quantifiable conversion.

The results illustrated in Table 3 indicate that in some cases successful catalytic turnover is dependent on the position of aromatic substitution. Notably, the disubstituted (3,4-dimethoxyphenyl)methanamine provided no conversion under the reaction conditions (entry 4). In contrast, the methoxyphenyl)methanamine (entry 2) displayed enhanced reactivity in comparison to its *tert*-butoxy-substituted analogue (entry 3). In all cases the first observed product was that of the *E* alkene. Upon further heating an increase in proportion of the *Z* alkene product (*E* stilbene) was apparent by ^{1}H NMR spectroscopy. This was most pronounced in the reactions with benzyl amine (entry 1) and 3,5-dimethoxybenzylamine (entry 5) whose *Z* alkene formation doubled upon further heating for the amount of time specified. It is well documented that *Z* stilbene readily isomerizes to *E* stilbene under thermal conditions.[19]

No hydroamination products were observed when the phenyl substituent of the 1-phenyl-2-(*o*-styrenyl)ethyne was replaced by H, Me, $SiMe_3$, or benzyl indicating the necessity of π-arene electron withdrawal in the insertive transition state. The presence of substituents on the exocyclic aromatic ring of the diarylacetylene functionality also led to a decrease in cyclic product formation in reactions with *n*-propylamine, irrespective of their electron donating or withdrawing character (Table 4, entries 1−3). These catalyses were also hindered by polymerization side reactions, which were most pronounced for the halogen-substituted substrates with the appearance of extremely broadened resonances in the alkyl region of the NMR spectra.

The 2,1 addition of the amine to the alkene component of the ene-yne substrate and the predominance of the *E*-alkene isomer of the THIQ product lead us to suggest the provisional mechanism illustrated in Scheme 2. Production of the

Table 4. Hydroamination of Aryl-2-(*o*-styrenyl)ethynes with *n*-Propylamine Catalyzed by III[a]

entry	amine	product	time (h)	conversion[b]
1		 **19**	62	47
2		 **20**	62	30
3		 **21**	72	24
4		-	24	-

[a]Reaction conditions: [cat]/[amine]/[substrate] = 1:10:20 in *p*-xylene-d_{10} at 130 °C, [amine] = 0.33 M. [b]Determined by ^{1}H NMR.

phenethylamine intermediate **B** takes place before cyclization, indicating that intramolecular addition of Sr−C to the alkynyl group does not occur prior to protonolysis of species **A**. As its concentration increases, the amine **B** will compete effectively with the primary amine substrate to effect protonolysis and provide the necessary strontium amide species **C**. Intramolecular cyclization of **C** may then occur either through the formation and subsequent protonolysis of the illustrated alkyl strontium intermediate **D** or concerted insertion and substrate-assisted protonolysis reminiscent of that deduced in our previous mechanistic studies of magnesium and calcium-catalyzed intramolecular hydroamination.[15] Irrespective of the precise details of this process, protonolysis by **B** or residual amine substrate will release the *Z*-stilbene THIQ product **E**. This *Z*-stilbene in turn may isomerize to its *E*-isomer **F** under the thermal conditions of the catalysis.

In summary, intermolecular alkene hydroamination may be coupled with intramolecular alkyne hydroamination, catalyzed by inexpensive and abundant alkaline earth precatalysts to provide entry to a variety of THIQ frameworks. Although

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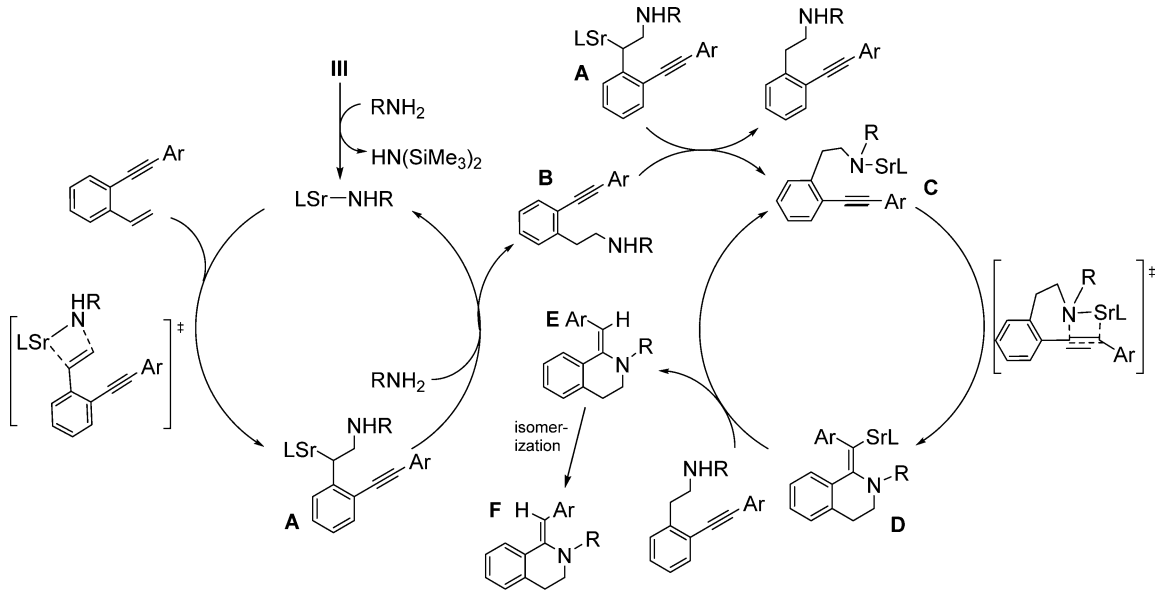
Scheme 2



limited to diaryl alkyne substitution, a broad reaction scope is available from variation of the primary amine reaction partner. The catalysis provides chemo- and regioselective C−N bond formation providing the corresponding exocyclic enamine products. The rich potential of this reactivity may be further emphasized by one pot elaboration of the enamine products, which could be reduced to the tetrahydroisoquinolines using $NaBH_4$ (compounds **22**−**37**, Supporting Information) or oxidized using iodosobenzene to the corresponding benzolactam (compound **38**, Supporting Information). Preliminary analysis suggests a dual cycle mechanism involving initial intermolecular alkene hydroamination and subsequent rate limiting alkyne insertion into the pendant Sr−N bond followed by rapid protonolysis to yield the cyclic enamine. We are continuing to elaborate upon this reactivity and to extend the substrate scope available to this atom-efficient domino process.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details for compounds **1**−**38** and characterization data. 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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