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

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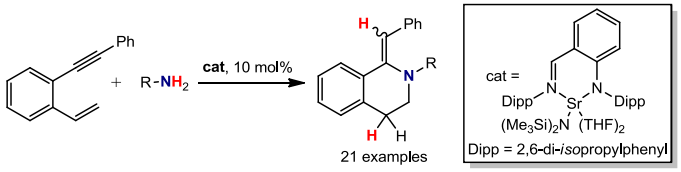
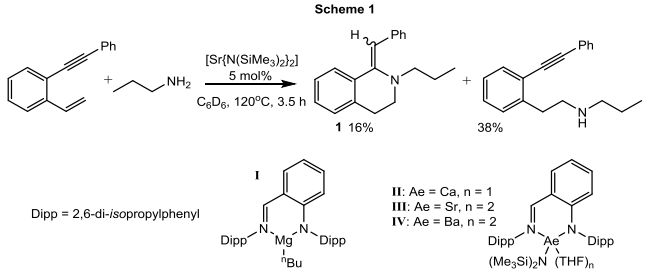
Supporting Information Placeholder



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 hydroamination and intramolecular alkyne hydroamination steps.

Tetrahydroisoquinoline (THIQ) ring systems are constituents of a wide range of alkaloids and synthetic organic compounds. Due to their important biological activities, for example as antibiotics, anti-tumor and antimicrobial agents,[1] methods for their preparation have become increasingly desirable over the past few decades.[2] The Bischler-Napieralksi, Pictet-Spengler and Pomeranz-Fritsch reactions are amongst the most long standing synthetic methods for the preparation of isoquinoline derivatives,[3] allowing the construction of the tetrahydroisoquinoline bicycles through imine intermediates and subsequent cyclization. Chiral Brønsted acid catalysts have also been applied to the enantioselective construction of THIQ skeleta. These methods include intramolecular oxetane ring opening,[4] multicatalytic three component coupling reactions with gold complexes,[5] oxetane directed aza-Diels-Alder reaction of indoles[6] and a reductive amination/aza-Michael sequence.[7] The development of enantioselective, catalytic acyl-Pictet-Spengler reactions[8] has also been achieved as well as calcium-catalyzed Pictet-Spengler reactions.[9] Notwithstanding their utility, each of these systems requires multi-step protocols and/or initial condensation reactions to provide the necessary imine intermediates. Whilst these methods provide access to synthetically useful substituted tetrahydroisoquinolines, catalytic routes to 1-benzyltetrahydroisoquinolines are scarce. 1-BnTHIQ derivatives possess significant biological activities[10] and associated alkaloids such as coclaurine and roefractine exhibit a broad range of pharmacological properties. These frameworks based on the *N*-substituted-1-benzyltetrahydroisoquinolines also provide platforms for important drug molecules.[11] 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]

Scheme 1



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.

Table 1: Hydroamination of 1-phenyl-2-(*o*-styrenyl)ethyne with *n*-propylamine catalyzed by **I** - **IV**.[a]

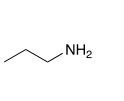
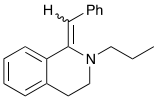
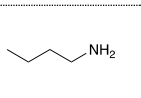
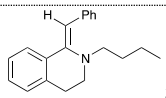
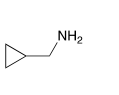
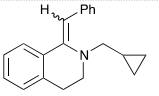
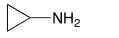
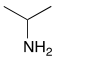
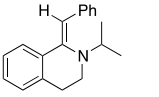
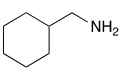
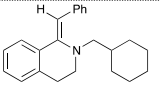
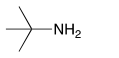
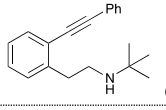
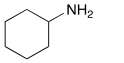
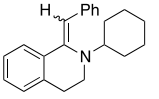
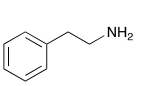
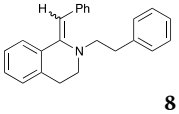
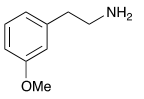
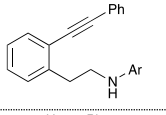
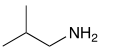
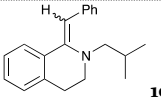
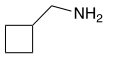
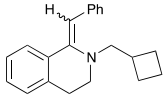
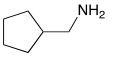
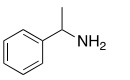
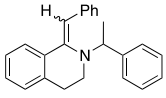
Entry	Cat.	Loading (mol%)	Time (h)	Conversion 1:X:amine (%)[b]
1	**I**	10	12	6:4:90
2[c]	**I**	10	43	23:12:65
3	**II**	5	16	32:68
4	**III**	5	16	43:57
5	**II**	10	15	71:29
6	**III**	10	14	99
7	**IV**	10	12	99

(a) Reaction conditions: 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.

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 the 40:20:1 ratio of substrate:amine:catalyst utilized by Marks for divinylbenzene hydroamination.[16] Whereas heating for an initial period of 14 hours 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 hours 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$_3$)$_2$}$_2$] pre-catalyst did not result in any viable yield of the cyclized product.

These encouraging observations prompted further development of the pre-catalyst 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 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 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.

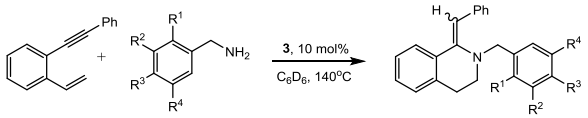
Consistent with the previous reports of Sarazin and co-workers, the catalytic activity was observed to increase with increasing atomic weight of the group 2 element employed. These effects are rationalized by extra rigidity encountered within the iminoanilide ligand framework in comparison to previously studied nacnac ligands.[15] The Mg pre-catalyst **I** displayed the lowest activity and was ineffective for the cyclization of the *N*-propylphenethylamine intermediate (entries 1 and 2). Although the Ba pre-catalyst **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 pre-catalyst synthesis, the strontium species **3** was, thus, selected for further study.

The scope of the hydroamination of 1-phenyl-2-(*o*-styrenyl)ethyne catalyzed by **III** was then examined with a range of commercially available primary alkyl amines (Table 2). Although effective cyclizations could be achieved using 5 mol % of **III,** use of 10 mol% of the pre-catalyst provided significantly increased conversions, especially with more sterically hindered alkyl amines. In all cases, the C-N bond forming processes were observed to occur with initial regioselective styrene hydroamination to provide the *anti*-Markovnikov product 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 quantative 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 ($NaBH_4$, see supporting information).

While the difference in activity between the *n*-propyl amine and *n*-butyl amine reactions is notable (entry 1 *versus* entry 2), intramolecular cyclization of the *N*-butyl phenethylamine intermediate was comparable to that of isopropylamine (entry 5). These observations indicate that the efficacy of the intramolecular insertion step is subtly dependent on the steric demands of the amine employed.

Comparison of the reactivity of cycloalkylmethylamines (entries 3, 6, 12 and 13) revealed a marked sensitivity to the ring size of the cyclic substituent. Whereas cyclopropylmethylamine was successfully cyclized (entry 3), the cyclopentyl-substituted methylamine displayed no evidence for even the formation of the alkene hydroaminationphenethylamine product (entry 13), even under more forcing conditions over 6 days, while the intermediate cyclobutylmethylamine provided only moderate conversion (entry 12). Presumably, the rate of cyclization of cycloalkanemethylamines depends on a balance between steric factors, ring strain and destabilizing effects encountered within the ring to allow a favorable conformation in the THIQ framework. Similarly, attempted cyclization with cyclopropylamine was unsuccessful whereas cyclohexylamine provided a modest production of the THIQ product (entries 4 and 8). In this case the cyclization may not be solely dependent on steric factors but more so the adoption of a favorable conformation by the relevant cycloalkyl ring (entries 4 and 5). 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 ascertained by ^{1}H NMR spectrosocopy to be 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. This again illustrates the steric impediment of such groups in the intramolecular insertion step.

Table 3: Hydroamination of 1-phenyl-2-(*o*-styrenyl)ethyne with substituted benzyl amines catalyzed by **III**.[a]

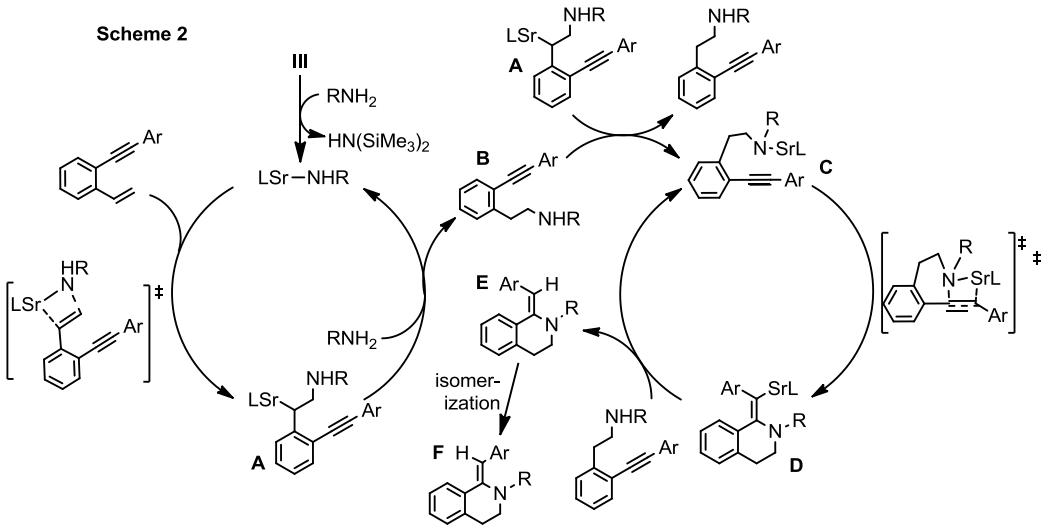


Entry	R^1	R^2	R^3	R^4	Time (h)	Conversion (%)[b]	E/Z[b]
1	H	H	H	H	12.5	99(**13**)	1.2:1
					29	99(**13**)	1:2
2[c]	H	H	OMe	H	10	68(**14**)	1:1.1
					15	72(**14**)	1:1.8
3	H	H	O^{t}Bu	H	13	55(**15**)	1:0.9
					28	63(**15**)	1:2
					12[c]	85(**15**)	1:2
4	H	OMe	OMe	H	12.5[d]	-	-
5	H	OMe	H	OMe	15	77(**16**)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

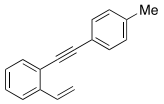
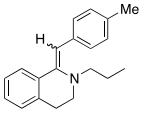
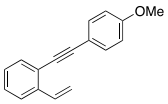
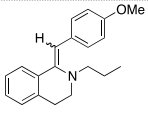
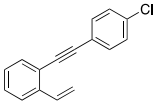
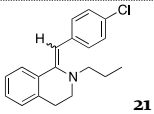
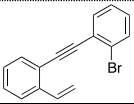
The results illustrated in Table 3 indicate that, although extension to the use of benzyl amines in this catalysis is broadly kinetically advantageous, in some cases successful catalytic turnover is dependent on the position of aromatic substitution. Notably, the di-substituted (3,4-dimethoxyphenyl)-methanamine provided no conversion under the reaction conditions (entry 4). In contrast, the

Scheme 2



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 corresponding to the *Z* stilbene backbone. Upon further heating with all benzyl amines an increase in proportion of the *Z* alkene product (*E* stilbene) was apparent by ^{1}H NMR spectroscopy accompanied by the decrease in *E* alkene product. 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]

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.

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 marked 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 and evident from the formation of dark green solutions and the appearance of extremely broadened resonances in the alkyl region of the NMR spectra. Although full conversion to the intermediate product was achieved for entries 1-3, the effect of aromatic substitution appeared to directly influence the subsequent rate of cyclization, presumably via electronic destabilizing effects with electron rich *para*-methyl and -methoxy substitution.

The initial chemoselective and aryl-directed 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. The observation that production of the phenethylamine intermediate **B** takes place before cyclization indicates 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** will then occur to form the alkyl strontium intermediate **D** which, through protonolysis by **B** or residual amine substrate, releases 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. Intermediates **B** and **C** were identified during spectroscopic monitoring of these reactions.

In summary, we have shown that intermolecular alkene hydroamination coupled with subsequent intramolecular alkyne hydroamination and catalyzed by inexpensive and abundant alkaline earth pre-catalysts provides entry to a variety of THIQ frameworks. Although limited to di-aryl

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 pr1otonolysis to yield the cyclic enamine. We are continuing to elaborate 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 interests.

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REFERENCES

1. (a) Bently, K. W. *Nat. Prod. Rep.* **2004**, *21*, 395-424; (b) Bently, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444; (c) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-1730.
2. Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
3. Whaley, W. M.; Govindachari, T. R. *Organic Reactions*; Wiley: New York, **1951**; Vol. 6, p 151.
4. Chen, Z.; Wang, Z.; Sun, J. *Chem, Eur. J.* **2013**, *19*, 8426.
5. Calleja, J.; González-Pérez, A. B.; de Lera, A. R.; Álvarez, R.; Fañanás, F. J.; Rodríguez, F. *Chem. Sci.* **2014**, 5, 996.
6. Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem. Int. Ed.* **2013**, 52, 2027.
7. Enders, D.; Liebich, J. X.; Raabe, G. *Chem. Eur. J.* **2010**, *16*, 9763.
8. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
9. Ven Eynden, M. J.; Stambulli, J. P. *Org. Lett.* **2008**, *10*, 5289.
10. Wasik, A.; Kajta, M.; Lenda, T.; A-Michaluk, L. *Neurotox. Res.* **2014**, *25*, 90.
11. (a) Gözler, B.; Kivçak, B.; Gözler, T. and Shamma, M. *J. Nat. Prod.* 1990, *53*, 666; (b) Hawkins, K. M. and Smolke, C. D. *Nat. Chem. Bio.* 2008, *4*, 564; (c) Cabedo, N.; Protais, P.; Cassels, B. K. and Cortes, D. *J. Nat. Prod.* 1998, *61*, 709.
12. (a) Wang, X-B.; Wang, D-W.; Lu, S-M.; Yu, C-B.; Zhou, Y-G.; *Tetrahedron: Asymmetry* **2009**, *20*, 1040; (b) Xie, J-H.; Zhu, S-F.; Zhou, Q-L. *Chem. Soc. Rev.* **2012**, *41*, 4126; (c) Yan, P-C.; Xie, J-H.; Hou, G-H.; Wang, L-X.; Zhou, Q-L. *Adv. Synth. Catal.* **2009**, *351*, 3243.
13. Brinkmann, C.; Barrett, A. G. M.; Hill, M. S. Procopiou, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 2193.
14. Haggins, J. *Chem. Eng. News* **1993**, *71*, 23.
15. Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670.
16. (a) Ryu, J.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* 2003, *125*, 12584; (b) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295-9306.
17. Liu, B.; Roisnel, T.; Carpentier, J.; Sarazin, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 4943.
18. Barrett, A. G. M.; Crimmin, M. R.; Hill, M. S.; Procopiou, P. A. *Proc. Roy. Soc. A.* **2010**, *466*, 927.
19. Kwasniewski, S. P.; Claes, L.; François, J. P.; Deleuze, M. S. *J. Phys. Chem.* **2003**, *118*, 7823.

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Table 1. Example of a Double-Column Table

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