JOC*Note*

pubs.acs.org/joc

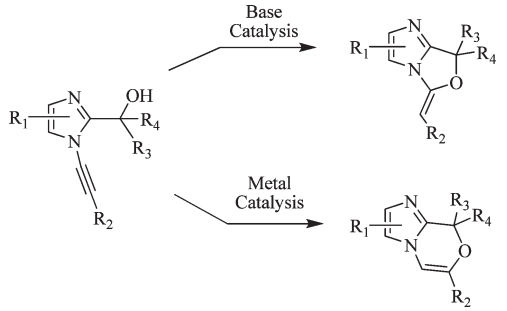
Efficient, Regioselective Access to Bicyclic Imidazo[1,2-*x*]- Heterocycles via Gold- and Base-Promoted Cyclization of 1-Alkynylimidazoles

Christophe Laroche and Sean M. Kerwin*

Division of Medicinal Chemistry, College of Pharmacy and Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

skerwin@mailutexas.edu

Received October 1, 2009



Reactions of 1-alkynylimidazoles involving the formation of their 2-lithio derivatives followed by addition of aldehydes or ketones are presented. The method gives access to 1-alkynyl-2-(hydroxymethyl)imidazoles which undergo 6-*endo-dig* or 5-*exo-dig* cyclization under $AuCl_3$- or base-catalyzed conditions to yield imidazo[1,2-*c*]-oxazoles and imidazo[2,1-*c*][1,4]oxazine heterocycles. Under transition metal catalysis, the reaction occurs in a regiospecific manner, leading exclusively to the product of 6-*endo-dig* attack, whereas under basic conditions, the reaction takes place in a regioselective manner giving preferentially the product from 5-*exo-dig* attack.

Imidazoles are an extremely important class of compounds with applications across all areas of chemistry,[1] biology,[2] and material science.[3] In particular, fused bicyclic imidazoles, both naturally occurring and synthetic, display a wide range of biological activities[4] and are found in a number of clinically important drugs.[5] There has been a growing interest in methods to efficiently access known fused imidazole frameworks[6] and to explore previously unreported chemotypes.[7] Yet, many fused bicyclic imidazole systems remain un- or under-explored.[6b]

One promising approach to the rapid elaboration of a wide variety of fused bicyclic imidazo[1,2-*x*] heterocycles, having a bridgehead imidazole nitrogen atom, focuses on the cyclization reactions of the relatively unexplored 1-alkynylimidazoles.[8] We recently reported a coupling reaction between imidazoles and bromoalkynes mediated by copper complexes allowing access to a wide range of these compounds.[9] The further functionalization of those 1-alkynylimidazoles at the 2 position by formation of their 2-lithio derivatives and subsequent treatment with various electrophiles has been studied.[10] The cyclization of 1-alkynylimidazoles containing appropriate nucleophilic groups at their 2 position can afford two types of bicyclic imidazoles depending upon the regiochemistry of the cyclization (Figure 1). Of particular interest is the degree to which the ynamine-like chemistry of the imidazole-substituted alkyne group plays a role in biasing the regiochemistry of this cyclization as well as the potential to control the regiochemistry by reagent selection using transition metals to activate the alkyne π-system.[11]

In exploring the 2-functionalization of the 1-alkynylimidazole **1a** by deprotonation and trapping of the anion with

(1) (a) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: New York, 1997; pp 1−143. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624.

(2) For review, see: De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1–23.

(3) (a) Moylan, C. R.; Miller, R. D.; Twieg, R. J.; Betterton, K. M.; Lee, V. Y.; Matray, T. J.; Nguyen, C. *Chem. Mater.* **1993**, *5*, 1499–1508. (b) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534.

(4) For recent examples, see: (a) Kim, P.; Kang, S.; Boshoff, H. I.; Jiricek, J.; Collins, M.; Singh, R.; Manjunatha, U. H.; Niyomrattanakit, P.; Zhang, L.; Goodwind, M.; Dick, T.; Keller, T. H.; Dowd, C. S.; Barry, C. E. *J. Med. Chem.* **2009**, *52*, 1329–1344. (b) Thompson, A. M.; Blasser, A.; Anderson, R. F.; Shinde, S .S.; Franzblau, S. G.; Ma, Z.; Denny, W. A.; Palmer, B. D. *J. Med. Chem.* **2009**, *52*, 637–545. (c) Wu, J.-P.; Emeigh, J.; Gao, D. A.; Goldberg, D. R.; Kuzmich, D.; Miao, C.; Potocki, I.; Qian, K. C.; Sorcek, R. J.; Jeanfavre, D. D.; Kishimoto, K.; Mainolfi, E. A.; Nabozny, G., Jr.; Peng, C.; Reilly, P.; Rothlein, R.; Sellati, R. H.; Woska, J. R., Jr.; Chen, S.; Gunn, J. A.; O'Brien, D.; Norris, S. H.; Kelly, T. A. *J. Med. Chem.* **2007**, *47*, 5356–5366. (d) Gehlert, D. R.; Cippitelli, A.; Thorsell, A.; Le, A.-D.; Hipskind, P. A.; Hamdouchi, C.; Lu, J.; Hembre, E. J.; Cramer, J.; Song, M.; McKinzie, D.; Morin, M.; Ciccocioppo, R.; Helig, M. *J. Neurosci.* **2007**, *27*, 2718–2726. (e) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 88–899. (f) Miwa, S.; Mizokami, A.; Keller, E. T.; Taichman, R.; Zhang, J.; Namiki, M. *Cancer Res.* **2005**, *65*, 8818–8825. (g) Dubuisson, M. L. N.; Ress, J.-F.; Marchand-Brynaert, J. *Drug Dev. Ind. Pharm.* **2005**, *31*, 827–849. (h) Chimirri, A.; Monforte, P.; Rao, A.; Zappala, M.; Monforte, A. M.; De Sarro, G.; Pannecouque, C.; Witvrouw, M.; Balzarini, J.; De Clercq, E. *Antiviral Chem. Chemother.* **2001**, *12*, 169–174.

(5) (a) Harrison, T. S.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65–89. (b) Basiuk, V. A. *Russ. Chem. Rev.* **1997**, *66*, 187–204. (d) Ansini, M.; Cappelli, A.; Vomero, S.; Giorgi, G.; Langer, T.; Bruni, G.; Romeo, R.; Basile, A. S. *J. Med. Chem.* **1996**, *39*, 4275–4284. (c) Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Vancutsem, J. *J. Med. Chem.* **1979**, *22*, 1003–1005.

(6) (a) Preston, P. N. *Condensed Imidazoles: 5−5 Ring Systems*; Wiley: New York, 1986; pp 1−46. (b) Hulme, C.; Lee, Y.-S. *Mol. Diversity* **2008**, *12*, 1–15. (c) Nodwell, M.; Pereira, A.; Riffell, J. L.; Zimmerman, C.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2009**, *74*, 995–1006. (d) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; Bridge, E.; Elsegood, M. R. J.; McInally, T.; McKee, V. *Tetrahedron* **2008**, *64*, 7745–7758. (e) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R. *J. Org. Chem.* **2007**, *72*, 3741–3749. (f) Chen, Y.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379–1382. (g) Hua, D. H.; Zhang, Z.; Chen, J. *J. Org. Chem.* **1994**, *59*, 5084–5087.

(7) (a) Krasavin, M.; Shkavrov, S.; Parchinsky, V.; Bukhryakov, K. *J. Org. Chem.* **2009**, *74*, 2627–2629. (b) Nowak, J.; Skalski, B.; Gdaniec, Z.; Milecki, J. *Tetrahedron Lett.* **2009**, *50*, 1671–1673. (c) Nayak, M.; Kanojiya, S.; Batra, S. *Synthesis* **2009**, 431–437. (d) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183–3186. (e) Le Bas, M.-D. H.; O'Shea, D. F. *J. Comb. Chem.* **2005**, *7*, 947–951.

(8) For cyclizations of 1,2-dialkynylimidazoles to imidazo[1,2-*a*]pyridines, see: Nadipuram, A.; Kerwin, S. M. *Tetrahedron* **2006**, *62*, 3798–3808.

(9) Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73*, 6462–6465.

(10) Laroche, C.; Kerwin, S. M. *Tetrahedron Lett.* **2009**, *50*, 5194–5197.

DOI: 10.1021/jo902073m Published on Web 11/09/2009

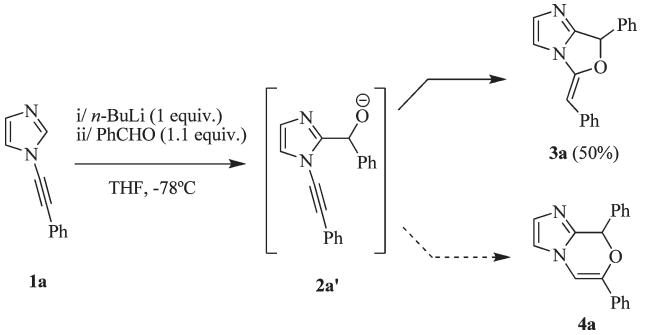
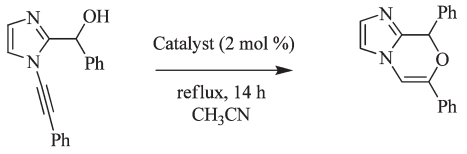


FIGURE 1. Regioselective one-pot conversion of **1a** to **3a**.

benzaldehyde, the formation of the 5,7-dihydroimidazo[1,2-*c*]oxazole **3a** was observed.[10,12] The structure of **3a** was confirmed by X-ray crystallography.[10] Interestingly, none of the 6-*endo-dig* cyclization product **4a** was present.[14]

A number of proposals have been put forth to rationalize the 5-*exo-dig* versus 6-*endo-dig* cyclization modes[13] of 4-ynols under basic conditions, including the double bond stereochemistry of the 5-*exo* cyclization products.[12,13,15] Recent studies have demonstrated alternative means to affect the regioselectivity of these cyclizations through metal catalysis.[16] However, it was not clear at the outset how applicable these precedents would be to the electronically biased 1-alkynylimidazole system **1a**. Thus, in order to explore the generality of the cyclization to **3a** and to develop a means of accessing the 6-*endo-dig* cyclization product **4a**, the isolation and characterization of the carbinol derived from the anion **2a**′ were undertaken.

TABLE 1. Catalyst Screen for *6-endo-dig* Cyclization



entry	catalyst	% conversion[a]	yield[b]
1	AuCl	100	90%
2	$AuCl_3$	100	95%
3	$PdCl_2$	70	60%
4	$PtCl_2$	0	–
5	$NiCl_2$	0	–
6	$CuCl_2$	100	90%
7	$BiCl_3$	0	–

[a]Based on recovered starting material. [b]Isolated yield after chromatography.

Compound **2a** (Table 1) can be isolated in 95% yield from the reaction of 1-alkynylimidazole **1a** under the conditions shown in Figure 1 when the reaction mixture is quenched with 1 M HCl solution rather than water. Treatment of alcohol **2a** in the presence of various metal catalysts in refluxing CH_3CN[17] was investigated (Table 1). The reaction proceeded to completion using $AuCl_3$ as catalyst affording imidazo[2,1-*c*][1,4]oxazine **4a** (Table 1, entry 2) as the only product in 95% isolated yield.[18]

In addition to $AuCl_3$, AuCl (Table 1, entry 1), $PdCl_2$ (Table 1, entry 3), and $CuCl_2$ (Table 1, entry 6) afforded the cyclized compound **4a**, although in lower yield. Interestingly, none of these cases showed any traces of the 5-*exo-dig* product **3a**.

Our interest in the formation of both compounds **3a** and **4a** led us to reinvestigate the cyclization reaction of **2a** under basic conditions. Under aqueous conditions (1 equiv of 1 M NaOH) in THF at room temperature, the desired compound **3a** was obtained in 75% yield. The use of strong organic bases (*n*-BuLi or EtMgBr) in THF did not lead to any conversion at room temperature and led to degradation under forcing conditions. A catalytic quantity of K_3PO_4 (5 mol %) in CH_3CN at reflux afforded **3a** in 80% yield within an hour. The cyclization was also attempted under acidic conditions (HCl saturated THF) with no success.[19] A few 5,7-dihydroimidazo[1,2-*c*]oxazole derivatives have been reported in the literature for their biological properties and are generally prepared by condensation reaction

(11) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (b) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (d) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodriguez-Garcia, I. *Chem. Rev.* **2008**, *108*, 3174–3198. (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (g) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (h) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309.

(12) For related 5-*exo-dig* cyclizations, see: (a) Chai, Z.; Xie, Z.-F.; Liu, X.-Y.; Zhao, G.; Wang, J.-D. *J. Org. Chem.* **2008**, *73*, 2947–2950. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703–1708. (c) Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110–6113.

(13) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–735. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482. (c) Sheng, Y.; Musaev, D. G.; Reddy, K. S.; McDonald, F. E.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 4149–4157.

(14) For reports of analogous, base-promoted 6-*endo-dig* cyclizations, see: (a) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697–9710. (b) Brennan, C. M.; Johnson, C. D.; McDonnell, P. D. *J. Chem. Soc., Perkin Trans. 2* **1989**, 957–961. (c) Garcia, H.; Iborra, S.; Primo, J. *J. Org. Chem.* **1986**, *51*, 4432–4436.

(15) (a) Nakatani, K.; Okamoto, A.; Saito, I. *Tetrahedron* **1996**, *52*, 9427–9446. (b) Houk, K. N.; Strozier, R. W.; Rozeboom, M. D.; Nagase, S. *J. Am. Chem. Soc.* **1982**, *104*, 323–325. (c) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798–8807. (d) Ivanchikova, I. D.; Usubalieva, G. E.; Schastnev, P. V.; N., E.; Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Bull. Int. Ed.* **1992**, *41*, 1672–1679. (e) Padwa, A.; Krumpe, K. E.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 5595–5603. (f) Nakatani, K.; Okamoto, A.; Yamanuki, M.; Saito, I. *J. Org. Chem.* **1994**, *59*, 4360–4361. (g) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1269–1275.

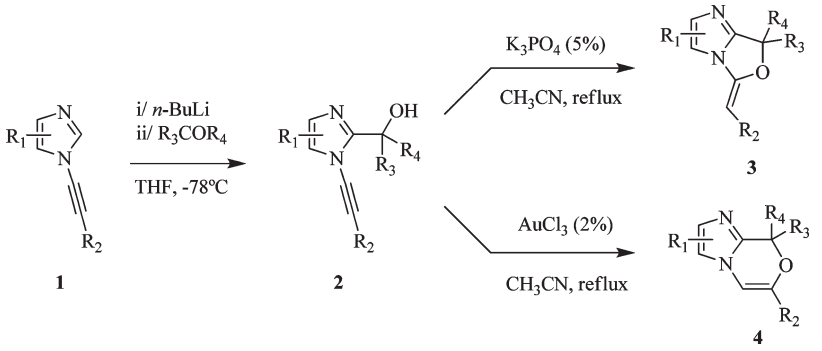
(16) (a) Ramana, C. V.; Mallik, R.; Gonnnade, R. G. *Tetrahedron* **2008**, *64*, 219–223. (b) Koo, B.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737–1740. (c) Liu, Y H.; Song, F. J.; Song, Z. Q.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412. (d) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (e) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949–4953. (f) Mzhelskaya, M. A.; Ivanchikova, I. D.; Polyakov, N. E.; Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 2798–2804. (g) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251–6259. (h) Qing, F.-L.; Gao, W.-Z. *Tetrahedron Lett.* **2000**, *41*, 7727–7730. (i) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687–7692. (j) Dalla, V.; Pale, P. *New J. Chem.* **1999**, 803–805. (k) Gabriele, B.; Salerno, G. *Chem. Commun.* **1997**, 1083–1084. (l) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966–5968. (m) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089–13102.

(17) Other solvents screened include CH_2Cl_2 (5% conversion with 2 mol % of $AuCl_3$ after 14 h) and THF (100% conversion and 60% yield of **4a** with 2 mol % of $AuCl_3$ after 14 h, with the formation of several unidentified side products).

(18) The imidazo[2,1-*c*][1,4]oxazine system has been reported previously only once: (a) Essassi, E. M.; Fifani, J.; Hamamsi, I. *Bull. Soc. Chim. Belg.* **1994**, *103*, 83–84. The related 6,8-dihydroimidazo[2,1-*c*][1,4]oxazines are also largely unexplored: (b) O'Sullivan, D. G.; Pantic, D.; Wallis, A. K. *Nature* **1965**, *205*, 262–264. (c) Medaer, B. P.; Hoornaert, G. J. *Tetrahedron* **1999**, *55*, 3987–4002.

(19) This led to a rapid conversion of **2a** into compounds arising from the addition of HCl across the carbon–carbon triple bond, as has been previously observed for 1-alkynylimidazoles; see refs 8 and 9.

TABLE 2. Regioselective Cyclizations of 1-Alkynylimidazoles 2a−j



entry	R_1	R_2	R_3	R_4	yield[a] (**1** to **2**)	yield[a] (**2** to **3**)	yield[a] (**2** to **4**)
1	H	Ph	H	Ph	**2a** (95%)	**3a** (80%)	**4a** (95%)
2	H	Ph	H	Et	**2b** (90%)	**3b** (97%)	**4b** (99%)
3	H	Ph	Ph	Et	**2c** (86%)	**3c** (99%)	**4c** (100%)
4	Benz[b]	Ph	Ph	H	**2d** (87%)	**3d** (96%)	**4d** (85%)
5	4-Ph-im[c]	Ph	Ph	H	**2e** (92%)	**3e** (78%)	**4e** (95%)
6	H	*p*-^{t}Bu-Ph	H	Ph	**2f** (92%)	**3f** (93%)	**4f** (100%)[d]
7	H	*p*-CF_3-Ph	H	Ph	**2g** (85%)	**3g** (85%)	**4g** (85%)[e]
8	H	TIPS	H	Ph	**2h** (90%)	**3h** (86%)	**4h** (0%)
9	H	H	H	Ph	**2i**[f]	**3i** (24%)	**4i** (16%)
10	H	*n*-Hex	H	Ph	**2j** (87%)	**3j**/**4j** (93%)[g]	**4j** (87%)

[a]Isolated yield after chromatography. [b]Benz refers to the benzimidazole core. [c]4-Ph-im refers to the (4-Ph)-imidazole core. [d]Yield after 1 h. [e]Yield after 6 days. [f]Yield from **2h** (TBAF, THF, −78 °C) is 80%. [g]**3j** and **4j** were obtained as a 53/47 mixture but can be separated by flash chromatography.

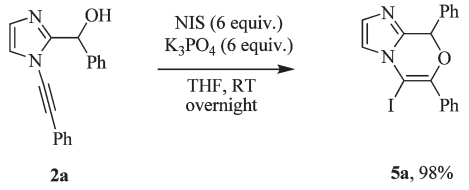


FIGURE 2. Iodo-cyclization of **2a** into **5a**.

between 2-(hydroxymethyl)imidazole and aldehydes.[20] However, 5-methylene-5,7-dihydroimidazo[1,2-*c*]oxazole derivatives such as **3a**, which possess a cyclic *N*,*O*-ketene acetal poised for further elaboration,[21] have not been previously reported.

In the same vein, the iodo-cyclization reaction of **2a** using excess of NIS and K_3PO_4 affords the iodo-imidazo[2,1-*c*]-[1,4]oxazine **5a** (Figure 2), which provides a chemical handle for further functionalization of the oxazine ring.[22,23]

Having optimized the conditions for the cyclization of **2a** in either the 5-*exo*-*dig* or the 6-*endo*-*dig* mode, the scope of these transformations was evaluated. Toward this end, compounds **2b**−**j** were synthesized, and their cyclizations were carried out in presence of $AuCl_3$ or K_3PO_4 in CH_3CN (Table 2).

Variation of the substituents at the carbinol center (R_3, R_4) and at the imidazole core (R_1) offered alcohols **2a**−**e** as well as the corresponding 5-*exo*-*dig* **3a**−**e** and 6-*endo*-*dig* **4a**−**e** cyclization products from good to excellent yields (Table 2, entries 1−5). Substrates possessing either an electron-donating (**2f**) or an electron-withdrawing (**2g**) aryl substituent on the carbon−carbon triple bond both led to the expected products in high yields (Table 2, entries 6 and 7); however, the rate of the $AuCl_3$-catalyzed cyclization was dramatically affected. The cyclization of the 4-methoxy substituent analogue **2f** in the presence of $AuCl_3$ is complete in just 1 h, whereas the cyclization of the (4-trifluoro)phenyl analogue **2g** requires 6 days before reaching completion. The cyclization of the triisopropylsilyl-substituted 1-alkynylimidazole **2h** occurred in the presence of K_3PO_4 to give **3h** in 86% yield; however, no conversion of **2h** into **4h** in the presence of $AuCl_3$ was observed even after extended reaction times (Table 2, entry 8). Apparently, the steric hindrance of the bulky TIPS substituent prevents approach of the hydroxyl group to the terminal sp carbon required for the 6-*endo*-*dig* cyclization. In the case of the 1-ethynylimidazole **2i**, prepared from **2h** by protodesilylation (TBAF, THF, −78 °C, 30 min), the corresponding 5-*exo*-*dig* **3i** and 6-*endo*-*dig* **4i** products were obtained in low yields (Table 2, entry 9). In these cases, the formation of multiple side products was observed. Finally, reaction of **2j** under basic condition is the sole example where a mixture of compounds has been obtained (Table 2, entry 10). Under gold catalysis, **2j** gave exclusively compound **4j** from 6-*endo*-*dig* attack. Remarkably, with the exceptions of compound **2h**, which failed to

(20) (a) Katritzky, A. R.; Aslan, D. C.; Leeming, P.; Stell, P. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1491–1500. (b) Katritzky, A. R.; Aslan, D. C.; Oniciu, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2245–2251. (c) Chimirri, A.; Monforte, P.; Zappalà, M.; Monforte, A. M.; De Sarro, G.; Pannecouque, C.; Witvrouw, M.; Balzarini, J.; De Clercq, E. *Antiviral Chem. Chemother.* **2001**, *12*, 169–174.

(21) For recent studies of cyclic *N*,*O*-ketene acetals, see: Zhou, A.; Cao, L.; Li, H.; Liu, Z.; Pittman, C. U., Jr. *Synlett* **2006**, 201–206. (b) Zhou, A.; Njogu, M. N.; Pittman, C. U., Jr. *Tetrahedron* **2006**, *62*, 4093–4102. (c) Huang, Y.-t.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536–6550. (d) Quast, H.; Ach, M.; Balthasar, J.; Hergenroether, T.; Regnat, D.; Lehmann, J.; Banert, K. *Helv. Chim. Acta* **2005**, *88*, 1589–1609.

(22) The structure of **5a** was confirmed by X-ray diffraction. **5a** was converted into **4a** by treating with magnesium followed by H_2O quench.

(23) Notably, Liu and co-workers reported compounds arising from a 5-*exo*-*dig* process under similar conditions: Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999–7002.

afford the 6-*endo-dig* cyclization product under $AuCl_3$ catalysis, and **2j**, which gave a mixture of **3j** and **4j** under basic condition, others alcohols **2** examined afforded exclusive 5-*exo-dig* cyclization in the presence of K_3PO_4 and exclusive 6-*endo-dig* cyclization in the presence of $AuCl_3$. We are unaware of a similar case of such high reagent control of both 5-*exo-dig* and 6-*endo-dig* cyclization modes in other 4-ynol cyclizations.

We believe that cycloisomerizations under basic and π-acid metal conditions are two distinct cases. Under basic condition, competition should take place between 5-*exo-dig* and 6-*endo-dig* cycloisomerization.[15e] With 1-alkynylimidazole substrates, the nitrogen attached on the carbon−carbon triple bond should strongly disfavor the formation of the carbionic species at its α-position (6-*endo-dig* attack). Under transition metal catalysis, a complete regioselective process regardless of the metal or the electronic nature of the substituents is observed. This indicates that, under transition metal catalysis, the 5-*exo-dig* attack is strongly disfavored.[13c] We propose that Au catalyzes the cycloisomerization by activation of the alkyne, for example, through a [(η^2-alkyne)-AuX_n] complex as recently described by Behrens.[24] This coordination results in preferential acceleration of the 6-*endo-dig* cyclization, possibly due to the proximity of the nucleophile to the alkyne terminal carbon in this proposed gold η^2 complex.

In conclusion, we have shown that 1-alkynyl-2-(hydroxymethyl)imidazoles can be cyclized in the presence of K_3PO_4 or $AuCl_3$ in CH_3CN to afford preferentially 5-*endo-dig* or exclusively 6-*endo-dig* cyclization products, respectively. These cyclizations exemplify a powerful new strategy for the construction of various imidazo-fused heterocycles from 1-alkynylimidazoles.

Experimental Section

Typical Procedure for the Synthesis of Phenyl-(1-(2-phenylethynyl)-1*H*-imidazol-2-yl)methanol (2a): To a solution of 1-(2-phenylethynyl)-1*H*-imidazole (**1a**) (168 mg, 1 mmol) in THF (10 mL) under argon at −78 °C was added *n*-BuLi (0.400 mL of 2.5 M solution in hexane, 1 mmol). The reaction mixture was stirred for 15 min at −78 °C prior to the addition of benzaldehyde (0.112 mL, 1.1 mmol). After stirring for 30 min at −78 °C, the mixture was quenched with 1 M HCl solution (5 mL) and the temperature was allowed to rise to room temperature. The reaction mixture was then extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (0−50% EtOAc/hexane) to afford 260 mg (95%) of **2a** as a white crystalline solid: mp 89.8−90.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.42 (2H, m), 7.39−7.28 (8H, m), 7.13 (1H, s), 7.00 (1H, s), 6.05 (1H, s), 4.39 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7 (br s), 140.3, 131.6 (2C), 129.0, 128.5 (2C), 128.4 (2C), 128.1, 127.6, 127.1 (2C), 122.3 (br s), 120.9, 77.1, 73.5, 69.5; IR (KBr) 3127, 2259, 1432, 1248, 1179, 1150, 1054, 758, 695 cm^{-1}; MS (CI) 549 (2M + 1, 4%), 531 (2M − 17, 8%), 275 (M + 1, 100%), 257 (M − 17, 23%); HRMS calcd for $C_{18}H_{15}N_2O$ (M + H$^+$) 275.1184, found 275.1181.

Typical Procedure for the Synthesis of (*Z*)-5-Benzylidene-7-phenyl-5,7-dihydroimidazo[1,2-*c*]oxazole (3a):. To a solution of **2a** (69 mg, 0.25 mmol) in CH_3CN (5 mL) was added K_3PO_4 (3 mg, 0.0125 mmol). The mixture was gently refluxed until completion. After chilling, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (0−20% EtOAc/hexane) to afford 55 mg (80%) of **3a** as a white solid: mp 107.6−109.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (2H, m), 7.52−7.46 (2H, m), 7.45−7.38 (3H, m), 7.36−7.30 (2H, m), 7.26−7.22 (2H, m), 7.20−7.14 (1H, m), 6.50 (1H, s), 5.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 144.1, 135.9, 135.1, 133.8, 129.4, 128.9 (2C), 128.5 (2C), 127.3 (2C), 126.6 (2C), 125.7, 110.3, 85.4, 80.1; IR (KBr) 3126, 1704, 1536, 1403, 1286, 1155, 1030, 996 cm^{-1}; MS (CI) 549 (2M + 1, 3%), 275 (M + 1, 100%), 257 (M − 101, 20%), 157 (M − 117, 40%); HRMS calcd for $C_{18}H_{15}N_2O$ (M + H$^+$) 275.1184, found 275.1186.

Typical Procedure for the Synthesis of 6,8-Diphenyl-8*H*-imidazo[2,1-*c*][1,4]oxazine (4a):. To a solution of **2a** (69 mg, 0.25 mmol) in CH_3CN (5 mL) was added $AuCl_3$ (0.5 mL of a 0.01 M solution in CH_3CN, 0.005 mmol). The mixture was gently refluxed until completion. After chilling, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (0−30% EtOAc/hexane) to afford 65 mg (95%) of **4a** as a white solid: mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (2H, m), 7.46−7.41 (2H, m), 7.41−7.32 (6H, m), 7.16 (1H, d, J = 1.4 Hz), 7.07 (1H, d, J = 1.4 Hz), 7.01 (1H, s), 6.49 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 139.6, 136.7, 131.9, 129.2, 128.9, 128.7, 128.5 (2C), 128.4 (2C), 127.1 (2C), 124.4 (2C), 115.6, 102.0, 76.1; IR (KBr) 3112, 1652, 1484, 1449, 1437, 1400, 1337, 1162, 1026, 749 cm^{-1}; MS (CI) 275 (M + 1, 100%); HRMS calcd for $C_{18}H_{15}N_2O$ (M + H$^+$) 275.1184, found 275.1185.

Acknowledgment. The Robert Welch Foundation (F-1298) and the Texas Advanced Research Program (3658-003) are thanked for financial support of this research.

Supporting Information Available: General experimental conditions, detailed experimental procedures, X-ray structure of **5a**, ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) Schulte, P.; Behrens, U. *Chem. Commun.* **1998**, 1633.