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Gold(I)-Catalyzed Rearrangement of *N*-Aryl 2-Alkynylazetidines to Pyrrolo[1,2-*a*]indoles

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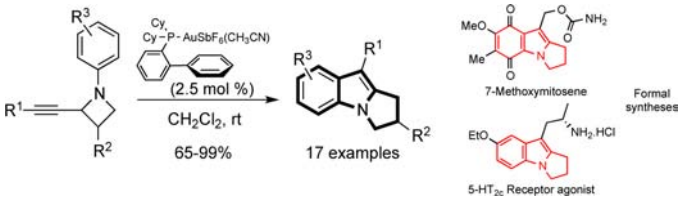
ABSTRACT



Various *N*-aryl-2-alkynylazetidines were very efficiently converted to pyrrolo[1,2-*a*]indoles with gold catalysts, especially the 2-biphenyl-dicyclohexylphosphino-gold(I) hexafluoroantimonate, in dichloromethane at room temperature. Additionally, two formal syntheses of bioactive non-natural compounds, i.e. 7-methoxymitosene and an 5-HT$_{2C}$ receptor agonist, have been achieved.

The now well-known activation of an alkene or alkyne by π-coordination with gold salts or complexes[1] and our involvement in gold multifaceted catalysis,[2] i.e. cascade reactions implying both π and σ Lewis acidities of gold,[3] led us to imagine a rapid access to pyrrolo[1,2-*a*]indoles **2**, based on the opening of *N*-aryl 2-alkynylazetidines **1** (Scheme 1). The process is based on π and σ Lewis acidities of gold, which could favor alkynylazetidine opening and allene formation (Scheme 1) (**A** and/or **A′** upon π or σ Au activation). The benzazocine intermediate **B** would then be cyclized upon another gold activation, leading after protodeauration of **C** to the pyrrolo[1,2-*a*]indole.

The pyrrolo[1,2-*a*]indole tricyclic structure is a common motif found in a number of naturally occurring products, among which mitomycins and its derivatives,[4] known as mitosanes and mitosenes,[5] are the most well-known due to their antitumor activities (Figure 1).[6] Yuremamine, isolated from the stem bark of *Mimosa hostilis*, is another recent interesting example, due to its traditional use promoting hallucinogenic and psychoactive effects.[7] Another psychoactive alkaloid harmalidine and its derivatives have been isolated from the seeds of *Pegalum harmala*.[8] The pyrrolo[1,2-*a*]indole motif can also be found in some non-natural compounds, exhibiting useful biological activities (Figure 1).[9,10] Due to their interesting properties, these compounds have given rise to various synthetic approaches.[11,12] Most of them relied on multistep sequences,

(1) For selected recent reviews on gold chemistry, see: (a) Lu, B.-L.; Dai, L.; Shi, M. *Chem. Soc. Rev.* **2012**, *41*, 3318. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, 1657. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, 1994. (d) Gagosz, F. *Actual. Chim.* **2010**, *347*, 12. (e) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075. (f) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

(2) (a) Kern, N.; Blanc, A.; Miaskiewicz, S.; Robinette, M.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2012**, *77*, 4323. (b) Kern, N.; Blanc, A.; Weibel, J.-M.; Pale, P. *Chem. Commun.* **2011**, *47*, 6665. (c) Britton, J.; Camp, J. E. *Chemistry Today* **2012**, *30* (3, Suppl.), 6.

(3) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

(4) (a) Kudo, S.; Marumo, T.; Tomioka, T.; Kato, H.; Fujimoto, Y. *Antibiot. Chemother.* **1958**, *8*, 228. (b) Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohonos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184. (c) Tulinsky, A. *J. Am. Chem. Soc.* **1962**, *84*, 3188.

(5) (a) Webb, S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidackas, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3185. (b) Webb, S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Lancaster, J. E.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidackas, C. *J. Am. Chem. Soc.* **1962**, *84*, 3187.

(6) (a) Bradner, W. T. *Cancer Treat. Rev.* **2001**, *27*, 35. (b) For the initially proposed but now proven mode of action, see: Iyer, V. N.; Szybalski, W. *Science* **1964**, *145*, 55.

(7) Vepsalainen, J. J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. *Planta Med.* **2005**, *71*, 1053.

(8) Siddiqui, S.; Khan, O. Y.; Siddiqui, B. S.; Faizi, S. *Phytochem.* **1987**, *26*, 1548.

(9) Peters, R.; Waldmeier, P.; Joncour, A. *Org. Process Res. Dev.* **2005**, *9*, 508.

(10) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877.

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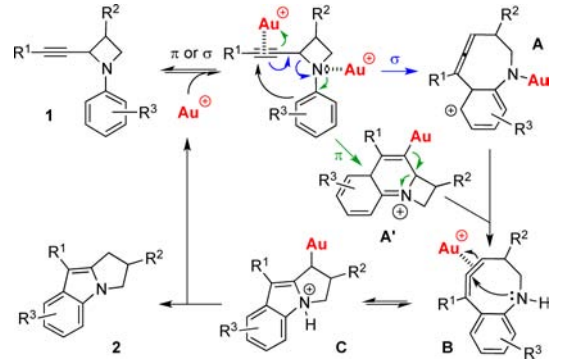
especially in the mitomycin area,[13] and any additional convergent and rapid route would be beneficial to this area.

Scheme 1. Hypothesis for Au-Catalyzed Conversion of *N*-Aryl Alkynylazetidines to Pyrrolo[1,2-*a*]indoles



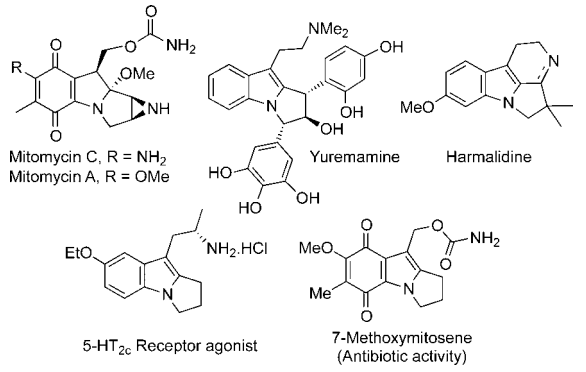
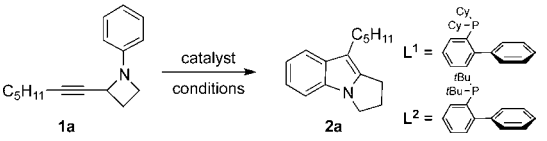


Figure 1. Natural products and some bioactive non-natural compounds exhibiting the pyrrolo[1,2-*a*]indole motif.

In the search for optimal conditions, the simple 2-(hept-1-ynyl)-2-methyl-1-phenylazetidine **1a** was readily prepared in three simple steps with a good overall yield (see Supporting Information) and submitted to various Au catalysts (Table 1).[14] Simple gold(I) or gold(III) chlorides gave the expected compound **2a** in dichloromethane in a clean reaction but with low conversions despite long reaction times (Table 1, entries 1−2). The more soluble and more electrophilic cationic phosphinogold(I) complexes showed a higher reactivity but a high dependence on solvent nature (entries 3−8).

Table 1. Screening of Reaction Conditions for the Au-Catalyzed Transformation of *N*-Phenyl 2-Alkynylazetidine **1a** into **2a**



entry	catalyst (mol %)	conditions[a]	time (h)	yield **2a** (%)
1	AuCl (4)	CH_2Cl_2, rt	18	45[b]
2	$AuCl_3$ (4)	CH_2Cl_2, rt	18	31[b]
3	PPh_3AuNTf_2 (4)	CH_2Cl_2, rt	1	80
4	″	$(CH_2Cl)_2$, rt	0.5	78
5	″	THF, rt	0.33	86
6	″	toluene, rt	18	37[b]
7	″	acetone, rt	18	65[b]
8	″	CH_3CN, rt	18	55[b]
9	L^1AuNTf_2 (4)	CH_2Cl_2, rt	0.5	92
10	L^1AuSbF_6.MeCN (4)	CH_2Cl_2, rt	0.33	98
11	L^2AuSbF_6.MeCN (4)	CH_2Cl_2, rt	2	98
12	L^1AuSbF_6.MeCN (**2.5**)	CH_2Cl_2, rt	**0.5**	**98**
13	$AgSbF_6$ (4)	CH_2Cl_2, rt	18	<10[c]

[a] C = 0.2 mol/L. [b] Conversion, the starting material accounting for the mass balance. [c] Degradation occurred leading to unidentified byproducts.

The Gagosz catalyst[15] rapidly gave **2a** in high yield in chlorinated solvents (Table 1, entries 3−4) or in THF (entry 5), but slow reactions and low conversions were observed in less polar solvents (entry 6) as well as in more polar and coordinating solvents (entries 7−8). Switching to the bulky and stabilizing (Cy_2)JohnPhos ligand $\mathbf{L^1}$ induced a fast and very efficient reaction (entry 9). Combining this ligand or the bulkiest JohnPhos ligand $\mathbf{L^2}$ and a more electrophilic counterion, such as SbF_6^-, gave almost *quantitatively* the pyrrolo[1,2-*a*]indole **2a** (entries 10−11) and allowed the catalytic charge to be decreased to only 2.5% (entry 12).[16] Control experiments showed that the silver salt used to prepare the cationic gold species was not responsible for the rearrangement, but led to degradation (entry 13).

With these results in hand, the scope of this gold(I)-catalyzed rearrangement of *N*-aryl 2-alkynylazetidines to pyrrolo[1,2-*a*]indoles was then examined. Various *N*-aryl 2-alkynylazetidines, **1a**−**j**, were thus prepared and submitted to the optimal conditions described above (Table 2).

Steric and electronic effects at the acetylene moiety on one hand and electronic effects at the *N*-aryl group on the other hand should influence the first opening-cyclization step and would thus shed some light on the actual mechanism (see Scheme 1). Their role was thus examined with substrates **1a**−**c** and **1d**−**g**. A branched alkyl chain next to the acetylene moiety did not significantly change the

(11) For selected references on the synthesis of pyrrolo[1,2-*a*]indoles, see: (a) Chen, K.; Zhang, Z.; Shi, M. *Chem. Commun.* **2012**, *48*, 7696. (b) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706. (c) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820.

(12) For a leading reference on yuremamine synthetic studies, see: Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 3497.

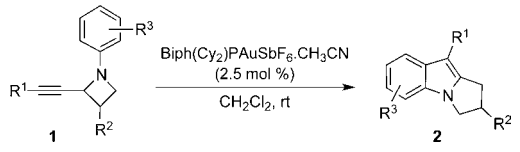
(13) For a review on mitomycin synthesis, see: (a) Andrez, J.-C. *Beilst. J. Org. Chem.* **2009**, *5*, n°33.

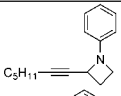
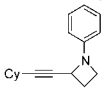
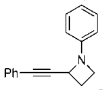
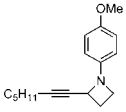
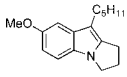
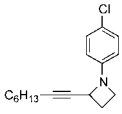
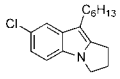
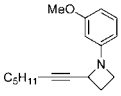
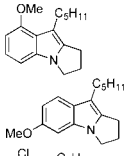
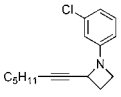
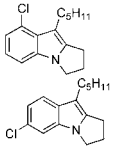
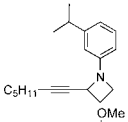
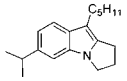
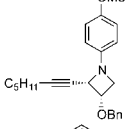
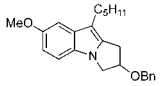
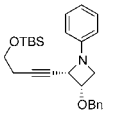
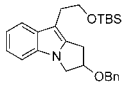
(14) For gold-catalyzed formation of pyrrolo[1,2-*a*]indoles, see: (a) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. (b) Yan, Z.-Y.; Xiao, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8624.

(15) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

(16) A further decrease in catalyst amount led to slower reactions (e.g., with 1%, the reaction required almost 10 days to give a 64% conversion, but still in a spot-to-spot transformation).

Table 2. Scope of the Gold(I)-Catalyzed Formation of Pyrrolo[1,2-*a*]indoles from *N*-Aryl 2-Alkynylazetidines



entry	alkynylazetidines, **1**	pyrrolo[1,2-*a*]-indoles, **2**	time (h)	yield (%)
1	 **1a**	 **2a**	0.5	98
2	 **1b**	 **2b**	0.5	91
3	 **1c**	 **2c**	2	80[a]
4	 **1d**	 **2d**	0.5	99
5	 **1e**	 **2e**	1	82
6	 **1f**	 **2f** 1:1 **2f'**	0.5	83
7	 **1g**	 **2g** 1:4 **2g'**	1	92
8	 **1h**	 **2h**	0.75	91
9	 **1i**	 **2i**	3	91[b]
10	 **1j**	 **2j**	3	82[b]

[a] Reaction run at 40 °C to complete the conversion. [b] Reaction run at 0 °C to avoid degradation.

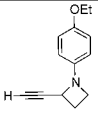
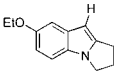
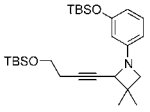
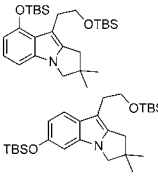
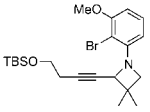
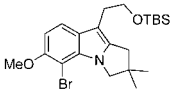
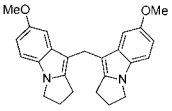
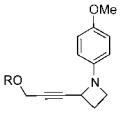
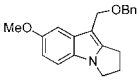
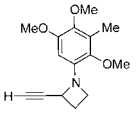
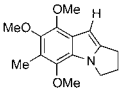
reaction rate compared to the simple linear alkyl group (Table 2, entry 2 vs 1). With a phenyl group conjugated with the acetylene moiety, the reaction proceeded as well, although the isolated yield was lower due to product instability (entry 3 vs 1). With an electron-donating group at the *para* position relative to the azetidine nitrogen, the rearrangement proceeded as rapidly but very efficiently (entry 4) while an electron-withdrawing group slightly slowed the reaction leading to a lower isolated yield (entry 5). With an electron-donating or -withdrawing group at the *meta* position relative to the azetidine nitrogen, mixtures of rearranged products were obtained (entries 6−7). The methoxylated derivative reacted more rapidly than its chlorinated analog, but a better yield was obtained with the latter, suggesting contradictory electronic influences. However, regioisomeric ratios were different, from 1:1 for a methoxy group to 1:4 for the chloro substituent (entry 6 vs 7). In the latter, the major product was the 3-chloro-9-pentylpyrrolo[1,2-*a*]indole **2g′**, the less hindered isomer, suggesting that steric interactions influenced the reaction. To conclude on these aspects, the *meta*-isopropyl derivative **1h** was rearranged under standard conditions (entry 8). A single regioisomer was observed and isolated in high yield, characterized as the 3-isopropyl-9-pentylpyrrolo[1,2-*a*]indole **2h**, again the less hindered isomer. These results thus confirmed the major role of steric interactions in this rearrangement, probably during the first arylation step (Scheme 1) in which the *meta*-aryl substituent would experience 1,3-allylic strain with the acetylenic substituent. We were able to ensure that β-substitution of the azetidine did not affect the reaction. As expected, the rearrangement of *cis*-**1i**−**j** very efficiently afforded the corresponding tricyclic indoles in high yields, although this reaction has to be performed at 0 °C to avoid OBn elimination (entries 9−10).

To go further, and with total synthesis perspectives,[17] we applied this Au-catalyzed rearrangement toward a few pyrrolo[1,2-*a*]indoles, either known intermediates in the synthesis of bioactive compounds or models of natural products (Table 3). We selected 7-ethoxy-2,3-dihyropyrrolo-[1,2-*a*]indole,[9] an intermediate en route to an agonist of the 5-HT_{2c} receptor (Figure 1), linked to the regulation of food intake and anxiety.[18] This compound could easily be obtained through the Au-catalyzed rearrangement of the simple *N*-(4-ethoxyphenyl)-2-ethynylazetidine **1k** in 85% yield (Table 3, entry 1). Yet, the psychoactive alkaloid harmalidine[19] seemed to have never been synthesized (Figure 1). The present Au-catalyzed rearrangement would offer the *first* approach to such a compound and analogs, starting from either *N*-(aryl) 2-(4-hydroxybut-1-ynyl)-3,3-dimethylazetidine **1l** or **1m**. The hindered *tert*-butyldimethylsilyl-protected derivative **1l** gave **2l** and **2l′** in good yield but as a 1:1 mixture (entry 2). To obtain the required regioselectivity toward the harmalidine core, we introduced a bromo substituent (**1m**), blocking one ortho position. The latter indeed furnished the expected regioisomer in good yield (entry 3). Looking for the mitomycins skeleton formation, we then engaged the free and TIPS-protected propargyl alcohols **1n** and **1o** in the gold-catalyzed rearrangement. We rapidly observed the formation of the same compound in both reactions (entries 4−5), which was identified as the 3,3′-methylbispyrrolo[1,2-*a*]indole **3** coming from the condensation of the desired pyrrolo[1,2-*a*]-indole motif on itself followed by a loss of formaldehyde.[20]

(17) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448.
(18) Tecot, L. H.; Sun, L. M.; Akana, S. F.; Strack, A. M.; Lowenstein, D. H.; Dallman, M. F.; Julluis, D. *Nature* **1995**, *374*, 542.
(19) Siddiqui, S.; Khan, O. Y.; Siddiqui, B. S.; Faizi, S. *Phytochem.* **1987**, *26*, 1548.

Rewardingly, the benzyl protected analog **1p** gave the expected carbon core **2p** of the mitomycin family, stable enough to be isolated in good yield (entry 6). Finally, the simple mitosene derivative **2q** was efficiently produced from 2-ethynyl-1-(2,4,5-trimethoxy-3-methylphenyl)-azetidine **1q**, although forcing conditions had to be used (entry 7). This result achieved the formal synthesis of the bioactive 7-methoxymitosene[21] (Figure 1).

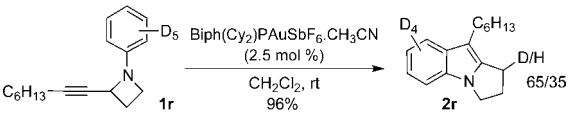
Table 3. Gold(I)-Catalyzed Formation of Pyrrolo[1,2-*a*]indoles of Biological Interest[a]

entry	alkynylazetidines, **1**		pyrrolo[1,2-*a*]indoles, **2**		yield (%)
1		**1k**		**2k**	85
2		**1l**		**2l** / **2l'** 1.1:1	66
3		**1m**		**2m**	70[b]
4		**1n**[c]		**3**	58[f]
5		**1o**[d]			47[f]
6		**1p**[e]		**2p**	65[f]
7		**1q**		**2q**	80[b]

[a] Performed with (Cy_2)JohnPhosAuSbF$_6$·MeCN (4 mol %) at rt in CH_2Cl_2. [b] Performed with JohnPhosAuSbF$_6$·MeCN (10 mol %) at 80 °C. [c] R = H. [d] R = TIPS (triisopropylsilyl). [e] R = Bn (benzyl). [f] Isolated yields after 72 h of stirring using 10 mol % of catalyst added in four portions.

To gain insight into the proposed mechanism,[22] we prepared the perdeuterated compound **1r** and monitored the deuterium labeling into the rearranged product **2r** (Scheme 2). In the latter, a single deuterium label was found at the allylic position within the pyrrolidine ring, at

Scheme 2. Deuterium Distribution in Product **2r** from Labeled Compound **1r**



the expected position of the gold atom after rearrangement (**C**, Scheme 1). This result corroborates the second part of the proposed mechanism, although the allyl gold part in **C** seems to not be protodemetalated through an SE′ mechanism as recently reported.[23]

However, the first step is still unclear. On one hand, cyclizations of propargyl anilines initiated by π-coordination have been reported.[24] Such a pathway would lead to **A′** in our case. On the other hand, the alkynyl azetidine opening can also be viewed as a gold-catalyzed amino-Claisen rearrangement, according to a few precedents in the literature.[25] The strain release of the four-membered ring would thus be the driving force of this process, and azaphilic gold interaction would initiate such a pathway leading to **A**, in analogy to very recent calculations performed for gold(I)-catalyzed Claisen rearrangement.[26] The fact that β-lactams, precursors of the azetidine derivatives (see Supporting Information), failed to give pyrrolo[1,2-*a*]-indolones supports the azaphilic activation pathway (**A** in Scheme 1), as in this case the carbophilic mechanism should have been favored by the weakly donating nitrogen.

In conclusion, we have developed a novel and efficient Au-catalyzed rearrangement of *N*-aryl-2-alkynylazetidines to pyrrolo[1,2-*a*]indoles. Further investigations of this rearrangement and applications in alkaloid synthesis are ongoing in our laboratory. In the latter aspect, two formal syntheses (5-HT$_{2C}$ receptor agonist and 7-methoxymitosene) have been achieved.

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Supporting Information Available. Complete experimental procedures, characterization data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1996**, *61*, 9055.
(21) Liang, L.; Wang, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 3736.
(22) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.
(23) Hasmi, A. S. K.; Schuster, A. M.; Litters, S.; Rominger, F.; Pernpointner, M. *Chem.—Eur. J.* **2011**, *17*, 5661.
(24) (a) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901. (b) Nevado, C.; Echavarren, A. *Chem.—Eur. J.* **2005**, *11*, 3155.
(25) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (b) Tejedor, D.; Mendez-Abt, G.; Cotos, L.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2013**, *42*, 458. For a gold-catalyzed tandem Claisen-cyclization reaction, see: (c) Sherry, B. D.; Maus, L.; Lafortza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. (d) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.
(26) Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2013**dx.doi.org/10.1021/jo302152j.

The authors declare no competing financial interest.