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Alternate Mode of Palladium-Catalyzed Alkynyliminium Ion Cyclizations Affording Stereodefined *N*-Alkyl-3-alkylidenepyrrolidines

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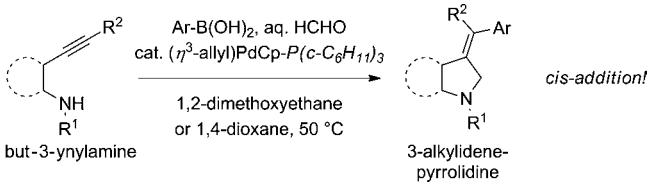
ABSTRACT



Pd/P(*c*-C_6H_{11})$_3$-catalyzed alkynyliminium ion cyclization in the presence of organoboronic acids affords stereodefined *N*-alkyl-3-alkylidenepyrrolidines. The distinctive *cis*-selective addition of the boronic acids and the iminium ions across the alkyne would result from favored 5-*exo*- or 6-*exo*-*dig* cyclization through oxidative addition of the formaldiminium ions to Pd(0).

Transition-metal-catalyzed carbocyclization of alkynes and alkenes is a powerful one-step method to prepare biologically important carbo- and heterocycles.[1] Carbocyclizations of alkynes bearing a carbonyl and related functionality have received scattered attention because it was believed that formation of π-complexes between the carbon−heteroatom π-bond and transition-metal catalysts was unfavorable.[2] However, these carbocyclizations can, in fact, be accessed using organometallic reagents under appropriate conditions. Their proposed reaction mechanisms are divided into the following three classes: (1) 1,2-addition of the alkenylmetal intermediate, which is generated in situ by the regioselective alkyne insertion between R−Rh(I)[3] or R−Pd(II)[4] bonds formed by transmetalation (TM) to carbon−heteroatom multiple bonds (mechanism A); (2) oxidative metallacycle formation with low-valent transition metal catalysts such as Ni(0)[5] and Pd(0)[6] followed by TM and reductive elimination (RE) (mechanism B); (3) "*anti*-Wacker"-type oxidative addition[7] to Pd(0) and subsequent TM and RE, a method that was developed by our group (mechanism C).[8] In remarkable contrast to the reactions proceeding through mechanisms A and B,

(1) (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662. (b) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791–2805. (c) Sohel, S. M. A.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269–2281. (d) Zhang, D.-H.; Zhang, Z.; Shi, M. *Chem. Commun.* **2012**, *48*, 10271–10279.

(2) (a) Vicente, J.; Abad, J.-A.; Gil-Rubio, J. *J. Organomet. Chem.* **1992**, *436*, C9–C12. (b) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *21*, 3545–3546. (c) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089–4092. (d) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *21*, 3238–3239. (e) Tian, Q.; Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 339–347.

(3) (a) Okamoto, R.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54–55. (b) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217–224 and references therein.

(4) (a) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227–4230. (b) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131–5133. (c) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 108–111. (d) Wang, H.; Han, X.; Lu, X. *Tetrahedron* **2010**, *66*, 9129–9134.

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(6) Alkyne isocyanates allow the oxapalladacycle formation to give 3-alkylideneoxindoles. Miura, T.; Toyoshima, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 4887–4889.

(7) Camacho, D. H.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 1085–1088.

(8) Pd(0)-catalyzed carbocyclizations of alkyne-carbonyls. (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406–1407. (b) Tsukamoto, H.; Ueno, T.; Kondo, Y. *Org. Lett.* **2007**, *9*, 3033–3036.

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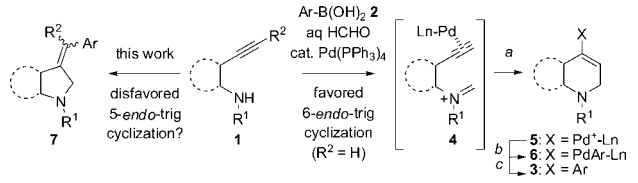
trans-selectivity observed in our carbocyclizations (through mechanism C) enabled 6-*endo*-*trig* cyclization of alkynyl iminium ions **4** generated in situ from but-3-ynylamines **1** and formaldehyde leading to 1,4-disubstituted 1,2,3,6-tetrahydropyridines **3** in the presence of organoboronic acids **2** (Scheme 1).[9]

Scheme 1. Pd(0)-Catalyzed Alkynyliminium Ion Cyclizations Leading to Tetrahydropyridine **3** and Pyrrolidine **7**

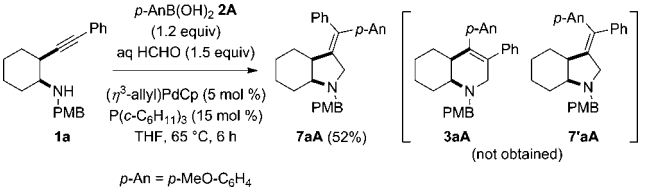


[a] 'anti-Wacker'-type oxidative addition. [b] transmetalation with **2**. [c] reductive elimination.

Despite their utility for diversity-oriented synthesis,[10] catalysts that promote the transformation of iminium **4** (or the corresponding imine of **1**) into a 5-membered heterocycle (i.e., pyrrolidine **7**) in either *cis* or *trans* fashion have not been found. The difficulty in accessing **7** has been ascribed to a disfavored 5-*endo*-*trig* cyclization through mechanisms A or C.[11−13] Thus, alternative reaction conditions to realize this transformation are needed.[14]

We endeavored to expand the scope of the Pd(0)-catalyzed three-component coupling reaction between but-3-ynylamines **1**, arylboronic acids **2**, and formaldehyde. We were surprised to discover that when amine **1a**, containing internal alkyne functionality, was subjected to *trans*-selective cyclization with *p*-methoxyphenylboronic acid (**2A**), the expected product, tetrahydropyridine **3aA**, was not observed (Scheme 2). Although no reaction took place with triphenylphosphine ligand, cyclization of **1a** was achieved with addition of the more σ-donating tricyclohexylphosphine ligand. This ligand was previously shown to be effective in *trans*-selective alkylative cyclizations of iminium ions derived from alk-4-ynals and external secondary amines.[8b] Surprisingly, NMR experiments on our cyclization product established its structure as pyrrolidine **7aA** resulting from *cis*-addition, while no *trans*-addition products (**3aA**, **7′aA**) were observed. We were intrigued by this result and motivated to investigate *cis*-selective arylative cyclization in detail. To the best of our knowledge, this is the first report on *cis*-selective alkyne−iminium ion cyclization.

Scheme 2. Unexpected *Cis*-Selective Arylative Cyclization of **1a** with **2A**



The *cis*-selective arylative cyclization of **1b** with **2A** required the presence of phosphine ligands containing at least one cyclohexyl group and the (η^3-allyl)PdCp catalyst (Table 1, entries 1−4). More σ-donating and sterically demanding tri-*tert*-butylphosphine and diphosphine were ineffective (entries 5 and 6). As expected, a substitution of (η^3-allyl)PdCp by Ni(cod)$_2$ afforded no cyclization product, and the absence of catalyst led to Petasis boronic acid−Mannich reaction[15] and *N*-methylation[16] (data not shown).[17] The minimal side reactions observed at 80 °C could be prevented by lowering the reaction temperature to 50 °C affording **7bA** in slightly higher yield (entries 4 vs 7). Among the solvents we tested, ethereal solvents including 1,2-dimethoxyethane (DME) and 1,4-dioxane (DOX) proved best (entries 7−10). With the optimized reaction conditions in hand, we examined the cyclization of **1b** with a wide variety of boronic acids.

The carbocyclization was compatible with *ortho*-substitution in the boronic acids (Table 2, entries 1 and 2). In contrast to the Pd(PPh$_3$)$_4$-catalyzed arylative cyclization of alkynyl iminium ions, unsubstituted- (**2D**) and electron-withdrawing group substituted (**2E**,**F**) phenylboronic acids did not retard the cyclization and gave **7bD**−**F** in good yields under the same reaction conditions (entries 3−5). Ketone and ester functionalities were also tolerated. Both electron-rich (**2G**,**H**) and electron-deficient (**2I**,**J**) heteroaryl boronic acids participated in the cyclization (entries 6−9). The cyclization reaction also took place with alkenylboronic acid **2K** to provide the 1,3-diene **7bK** (entry 10).

A secondary alkyl group on the nitrogen atom was also tolerated for the cyclization (Table 3, entry 3). The presence of an electron-donating methoxy group at the *para*-position to the ethynylbenzene in **1f** (entry 5) retarded the reaction, relative to entries 4 and 6, but good product yield

(9) Pd(0)-catalyzed carbocyclizations of alkyne− and allene−iminium ions: Tsukamoto, H.; Kondo, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 4851–4854.

(10) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.

(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(12) Nucleophile-promoted cyclizations of but-3-ynylamines occur in the endocyclic sense to afford 1,4-disubstituted 1,2,3,6-tetrahydropyridines: (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612–614. (b) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 5934.

(13) It is reported that propargylsilanes undergo 5-*endo*-*trig* cyclization with iminium ions generated in situ to give 3-vinylidene-*N*-alkylpyrrolidines under acidic conditions against Baldwin's rule: Damour, D.; Pornet, J.; Miginiac, L. *Tetrahedron Lett.* **1987**, *28*, 4689–4690.

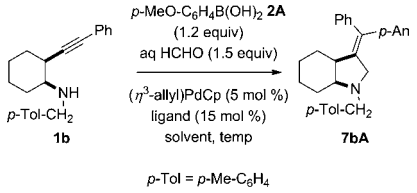
(14) 5-*Exo*-*dig* cyclization should be an alternative mode. Oxidative addition of carbamoyl chlorides and cyanoformamides to Pd(0) and the following alkyne insertion is used to prepare 3-alkylideneoxindoles. (a) Fielding, M. R.; Grigg, R.; Urch, C. J. *Chem. Commun.* **2000**, 2239–2240. (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711–2713.

(15) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.

(16) Formic acid generated in situ by disproportion of formaldehyde may cause Eschweiler−Clarke methylation. An acid catalyst is reported to promote the disproportion: Ogorodnikov, S. K.; Filippova, V. A.; Blazhin, Y. M.; Vergunova, N. G.; Svetlova, L. M.; Mamontova, N. I. *Khim.-Farm. Zh.* **1987**, *21*, 862–866.

(17) Additionally, substitution of aqueous formaldehyde by paraformaldehyde and boronic acid by its neopentylglycol ester did not give better results.

Table 1. Ligand and Solvent Effects on Arylative Cyclization of **1b** with **2A**

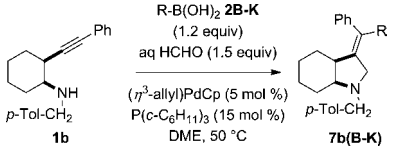


p-Tol = *p*-Me-C_6H_4

entry	ligand	solvent[a]	temp (°C)	time (h)	yield (%)
1	PPh_3	THF	80	4	trace[b]
2	$PPh_2(c\text{-}C_6H_{11})$	THF	80	1	71[b]
3	$PPh(c\text{-}C_6H_{11})_2$	THF	80	1	71[b]
4	$P(c\text{-}C_6H_{11})_3$	THF	80	2	61[b]
5	$P(t\text{-}Bu)_3$	THF	80	6	0
6	dppe[c]	THF	80	6	0
7	$P(c\text{-}C_6H_{11})_3$	THF	50	18	68
8	$P(c\text{-}C_6H_{11})_3$	DMF	50	6	68
9	$P(c\text{-}C_6H_{11})_3$	DOX	50	13	84
10	$P(c\text{-}C_6H_{11})_3$	DME	50	13	91

[a] THF, DMF, DOX, and DME stand for tetrahydrofuran, *N*,*N*-dimethylformamide, 1,4-dioxane, and 1,2-dimethoxyethane, respectively. [b] Small amounts of byproducts resulting from Petasis boronic acid–Mannich reaction and *N*-methylation were also observed. [c] dppe = 1,2-bis(diphenylphosphino)ethane.

Table 2. Cyclization of **1b** with Aryl-, Heteroaryl-, and Alkenylboronic Acids **2B**–**K**

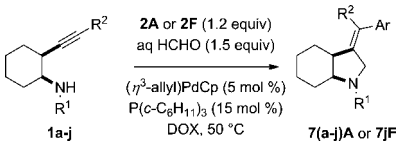


entry	R in **2**	**7**	time (h)	yield (%)
1	*o*-$MeOC_6H_4$ **2B**	**7bB**	16	88
2	*o*-MeC_6H_4 **2C**	**7bC**	16	79
3	C_6H_5 **2D**	**7bD**	24	85
4	*p*-$MeO_2CC_6H_4$ **2E**	**7bE**	16	66
5[a]	*p*-AcC_6H_4 **2F**	**7bF**	2	78
6[a]	2-thiophene **2G**	**7bG**	13	84
7	3-thiophene **2H**	**7bH**	17	66
8	2-methoxy-3-pyridyl **2I**	**7bI**	17	66
9	6-methoxy-3-pyridyl **2J**	**7bJ**	17	51
10	(*E*)-*β*-styrene **2K**	**7bK**	3	88

[a] Reaction in DOX instead of DME.

was maintained. Employment of $PPh(c\text{-}C_6H_{11})_2$ as ligand gave better results when alkenyl or alkyl groups are substituted on the alkyne terminus to give **7hA** and **7iA** in moderate yields (entries 7 and 8). Using either electron-rich or -deficient arylboronic acids, amine **1j**, containing a terminal alkyne, was cyclized under $Pd/P(c\text{-}C_6H_{11})_3$ catalysis to give pyrrolidine **7jA** and **7jF** as major products (entries 9 and 10).[18] This result suggests that the alkyne substituent is not essential for the *cis*-selective cyclization.

Table 3. Substituent Effects on Arylative Cyclization of **1a**–**j** with **2A** or **2F**[a]



entry	R^1	R^2	**7**	time (h)	yield (%)
1	PMB	Ph	**7aA**	15	90
2	$n\text{-}C_4H_9$	Ph	**7cA**	24	61
3	$i\text{-}C_3H_7$	Ph	**7dA**	15	65
4[b]	Bn	Ph	**7eA**	3	72
5	Bn	*p*-$MeOC_6H_4$	**7fA**	13	90
6[b]	Bn	*p*-$NO_2C_6H_4$	**7gA**	3	83
7[c]	*p*-$MeC_6H_4CH_2$	1-cyclohexenyl	**7hA**	24	57
8[c]	*p*-$MeC_6H_4CH_2$	$n\text{-}C_4H_9$	**7iA**	24	42
9	Bn	H	**7jA**	12	67[d]
10	Bn	H	**7jF**	12	40[e]

[a] Reaction with **2A** and **2F** for entries 1–9 and 10, respectively. [b] Reaction in DME instead of DOX. [c] Reaction with $PPh(c\text{-}C_6H_{11})_2$ instead of $P(c\text{-}C_6H_{11})_3$. [d] Combined yields with *trans*-addition product **3jA** (**7jA**:**3jA** = 5:1, ratio determined by ^1H NMR analysis). [e] Combined yields with *trans*-addition product **3jF** (**7jF**:**3jF** = 30:1, ratio determined by ^1H NMR analysis).

Tether effects on the cyclizations of but-3-ynylamines **1k**–**n** were briefly explored (Table 4). Although the arylative cyclization of *trans*-2-(phenylethynyl)cyclohexylamine **1k** was less efficient than its *cis*-isomer (**1b**), the *cis*-cyclopentyl homologue **1l** underwent the cyclization as efficiently (entries 1 and 2). More flexible tethers in but-3-ynylamines **1m** and **1n** reduced the product yields (entries 3 and 4). In addition, the corresponding primary amine, *N*-alkyl-2-(phenylethynyl)aniline, and aldehydes except for formaldehyde gave no cyclization product, which suggested that the *N*,*N*-dialkylformaldiminium ions generated in situ should be a key intermediate for the cyclization (data not shown).

A plausible mechanism for the $Pd/P(c\text{-}C_6H_{11})_3$-catalyzed *cis*-selective arylative cyclization of alkynyl formaldiminium ions generated from **1** is shown in Scheme 3. According to the reported regioselectivities of the carbometalation of phenyl-substituted alkynes,[2,4] 5-*endo*-*trig* cyclization through mechanism A is unlikely.[19] The Thorpe–Ingold effect[20] should play an important role to set the alkyne-coordinated Pd toward formaldiminium ion **8**, while *σ*-donating tricyclohexylphosphine ligand would allow oxidative addition of the iminium to Pd(0)[21] leading

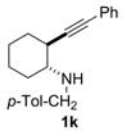
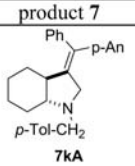
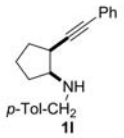
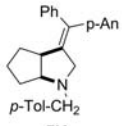
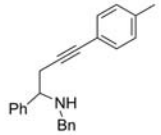
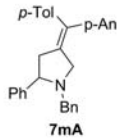
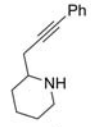
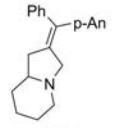
(18) In contrast to the cyclization of internal alkyne **1b**, use of PPh_3, $PPh_2(c\text{-}C_6H_{11})$, and $PPh(c\text{-}C_6H_{11})_2$ as ligands resulted in the conversion of **1j** to tetrahydropyridines **3j** as major products. The ratios of **7j** to **3j** slightly increase as cyclohexyl groups substitute phenyl groups in the phosphine ligands.

(19) $Pd(OAc)_2$(dppe), reported to be an appropriate catalyst for the reaction mechanism A, was ineffective for this cyclization.

(20) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

(21) A combination of (η^3-allyl)PdCp with an excess of phosphine ligand is known to produce phosphine-ligated Pd(0) species accompanied with reductive elimination of 5-allylcyclopenta-1,3-diene: Tatsuno, Y.; Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1979**, *19*, 220–223.

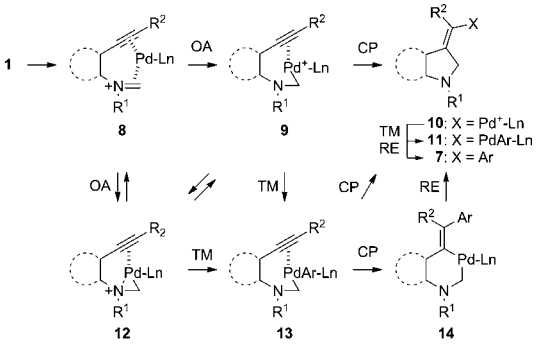
Table 4. Substrate Scope and Limitations

entry	substrate 1	product 7	time (h)	yield (%)
1[a]	 1k	 7kA	16	40
2[a]	 1l	 7lA	13	72
3[b]	 1m	 7mA	36	26
4[a, c]	 1n	 7nA	24	39

[a] Reaction in DOX. [b] Reaction in DME. [c] Reaction with 10 mol % of catalysts.

to aminomethylpalladium(II) **9**.[22,23] Either the less σ-donating triphenylphosphine-ligated Pd(0) or a substituted formaldiminium ion would retard this oxidative addition step. Subsequent insertion of the coordinated alkyne between the carbon−Pd bond in **9** would provide alkenylpalladium(II) **10**, which undergoes TM with arylboronic acid **2** and RE to give pyrrolidine **7** and Pd(0). An electron-withdrawing aryl-substituted alkyne would become susceptible to both coordination to the electron-rich Pd(0) and carbopalladation processes. The order of carbopalladation and TM would be interchangeable (**9** → **13** → **11** → **7**). The diorganopalladium(II) intermediate **13** may also be formed by TM between **2** and Pd(II)−CH_2−N three membered ring **12**,[22,24] which would be in equilibrium to (η^2-formaldiminium)Pd(0) complex **8** as well as **9**. Alternative alkyne insertion between the Ar−Pd bond in **13** followed by reductive elimination of **7** from palladacycle **14** is also possible.

Scheme 3. Plausible Mechanism for the Arylative Cyclization of **1**



OA: oxidative addition of iminium to Pd(0) catalyst guided by proximal alkyne. CP: carbopalladation. TM: transmetalation with **2**. RE: reductive elimination.

This study has uncovered the first example of a *cis*-selective alkyne−iminium ion cyclization leading to *N*-alkyl-3-alkylidenepyrrolidines. We have previously reported that similar reaction conditions afford tetrahydropyridines.[9] We now show that by simply varying the phosphine ligands for the Pd catalyst two diverse product scaffolds (tetrahydropyridines and pyrrolidines) can be obtained. Stereodefined tri- and tetrasubstituted olefins in the products can be further functionalized leading to highly complex heterocycles. The proposed cyclization mechanism, proceeding by oxidative addition of iminium ions to Pd(0), should be useful for devising methods to access other difficult organic transformations. Studies to elucidate more mechanistic details and expand the scope of the cyclization process are underway.

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

The authors declare no competing financial interest.

(22) Although Pd−(η^2-iminium) complexes like **9** and **12** have not, to our knowledge, been prepared by oxidative addition of the iminium ions to Pd(0), it can be prepared by activation of a C−H bond adjacent to the amine *N*-atom in trialkylamines with a Pd(II) complex: Lu, C. C.; Peters, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15818–15832.

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(24) $(Ph_3P)Ni(H_2C{=}NMe_2)Cl$, prepared by oxidative addition of $(H_2C{=}NMe_2)Cl$ to Ni(0) complexes, i.e., $(Ph_3P)_2Ni(C_2H_4)$ or $(Ph_3P)_4Ni$, undergoes a substitution reaction with cyclopentadienyl anion to give $(Ph_3P)Ni(CH_2NMe_2)Cp$, which contains a dimethylaminomethyl group σ-bonded to nickel: Sepelak, D. J.; Pierpont, C. G.; Barefield, E. K.; Budz, J. T.; Poffenberger, C. A. *J. Am. Chem. Soc.* **1976**, *98*, 6178–6185.