Heterocyclic Synthesis

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A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of (±)-Trachelanthamidine**

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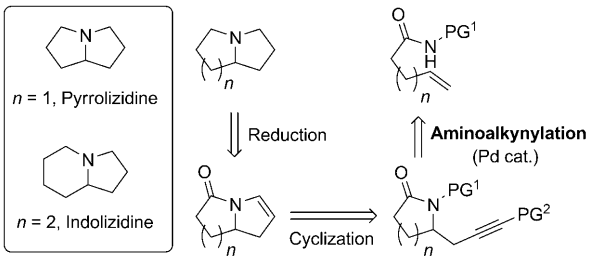
Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday

Nitrogen-containing heterocycles are omnipresent in natural products and biologically active compounds. Among them, pyrrolizidine and indolizidine alkaloids have attracted broad interest for their potential pharmacological applications. Furthermore, their polycyclic structures, which frequently incorporate multiple chiral centers, have been the testing ground for new C–C and C–N bond-forming methods for several decades.[1]

In this context, we envisaged a novel strategy to access both pyrrolizidine and indolizidine heterocycles involving the initial aminoalkynylation of olefins to afford 5-propargyl lactams (Scheme 1). This step allows both C–N bond formation and introduction of the two missing carbon atoms in a single transformation. The amination of olefins is still a major challenge in organic synthesis and only recently progress has been realized in intramolecular hydroamination,[2] the aza-Wacker reaction,[3] and more challenging multiple aminofunctionalization of alkenes.[4] In particular, the simultaneous formation of C–N and C–C bonds has been focused mostly on aminoarylation and aminocarbonylation. In this context, the aminoalkynylation process is still unknown, despite its tremendous potential for further functionalization. In 2010, our research group reported the intramolecular oxyalkynylation of alkenes.[5] However, we were unable to use our protocol efficiently in the case of amination. The second required cyclization could be envisaged through hydroamination of the triple bond,[2,6] or a two-step alternative route through vinyl halides.[7] Both approaches are well established for the intermolecular synthesis of enamides, but they have never been reported to access pyrrolizidinones or indolizidinones.



Scheme 1. Strategy for the synthesis of pyrrolizidines and indolizidines. PG = protecting group.

Herein, we report the exceptional efficiency of lithium palladate catalysts for the intramolecular aminoalkynylation of olefins using hypervalent iodine reagents. The reaction is broadly applicable, working not only for γ- and δ-lactams but also for oxazolidinones, imidazolidinones, and indole or pyrrole piperazinones. The importance of the aminoalkynylation reaction is demonstrated in the elaboration of the lactam acetylenes into pyrrolizidines and indolizidines using a two-steps procedure (indium-mediated iodination[8] and copper-catalyzed vinylation),[7c,d] which culminated in the total synthesis of the natural product (±)-trachelanthamidine.

A preliminary screening was performed by subjecting protected/activated amides derived from 4-pentenoic acid to the protocol developed for oxyalkynylation (triisopropylsilyl ethynylbenziodoxolone (TIPS-EBX (**2a**)), 10 mol% of [Pd(hfacac)$_2$], dichloromethane).[5,9] *N*-tosyl amide **1a** was the most promising substrate, but the yield was low (33%) because of decomposition (Table 1, entry 1).

Optimization of the reaction conditions using the previously discovered catalyst was not successful.[10] An interesting lead result was obtained with $PdCl_2$ in EtOH (Table 1, entry 2). Better yields were observed with LiCl as the additive (Table 1, entry 3), while other Li or Cl salts were less efficient (Table 1, entries 4 and 5). Three equivalents of LiCl with respect to **2a** was optimal (Table 1, entry 6). Under these reaction conditions, the active catalyst could be $Li_2[PdCl_4]$ formed in situ. Indeed, when $Li_2[PdCl_4]$ was used as the catalyst with **1a**, product **3a** was isolated in the same yield as when $PdCl_2$/LiCl was used (Table 1, entry 7).[11] One possible explanation for this effect would be that halide ions can slow down side reactions, in particular β-hydride elimination.[12] To the best of our knowledge, this is the first example of the use of a palladate complex for the carboamination of olefins. The reaction was performed at room temperature using analytical grade EtOH in an ambient atmosphere. Contributing factors that make this method highly practical are: LiCl is inexpensive, $PdCl_2$ is the most commonly used Pd salt, and TIPS-EBX (**2a**) is commercially available. The use of EBX reagents

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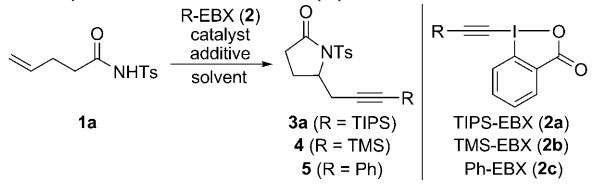
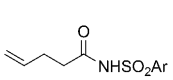
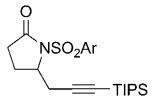
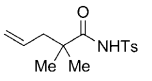
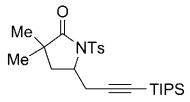
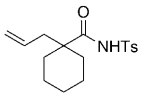
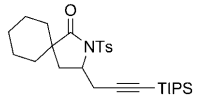
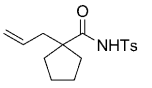
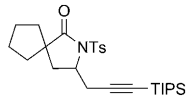
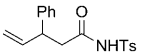
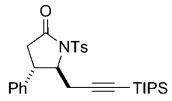
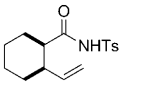
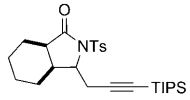
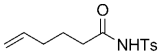
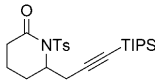
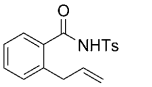
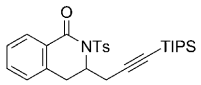
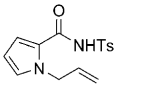
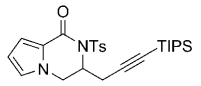
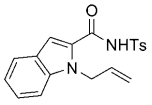
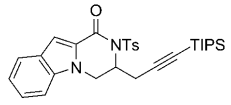
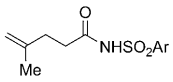
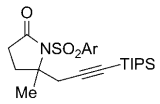
Table 1: Optimization of the aminoalkynylation reaction.[a]



Entry	R	Catalyst	Additive	Solvent	Yield [%][b]
1	TIPS	$[Pd(hfacac)_2]$	–	CH_2Cl_2	33
2	TIPS	$PdCl_2$	–	EtOH	57
3	TIPS	$PdCl_2$	LiCl	EtOH	76 (75)[c,d]
4	TIPS	$PdCl_2$	Bu_4NCl	EtOH	48
5	TIPS	$PdCl_2$	$LiBF_4$	EtOH	20
6[e]	TIPS	$PdCl_2$	LiCl	EtOH	88
7[c]	TIPS	$Li_2[PdCl_4]$	–	EtOH	84[d]
8[e]	TMS	$PdCl_2$	LiCl	EtOH	23
9[e]	Ph	$PdCl_2$	LiCl	EtOH	58

[a] Reaction conditions: 0.069 mmol of **1a**, 0.014 mmol of catalyst, 0.084 mmol of R-EBX (**2**), 0.084 mmol of additive in 1.75 mL of solvent, 15 h, RT. [b] Yield was determined by ^{1}H NMR spectroscopy. [c] Using 0.40 mmol of **1a**, 0.040 mmol of catalyst, 0.48 mmol of R-EBX (**2**), 0.48 mmol of additive in 10 mL of solvent, 3.5 h, RT. [d] Yield of isolated product. [e] As for [c], but using 1.44 mmol of LiCl. Yield of isolated product. hfacac = hexafluoroacetylacetonate, TIPS = triisopropylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

Table 2: Aminoalkynylation of activated amides.[a]

Entry	Substrate		Product		Yield [%][b]
					
1	**1a**	Ar = 4-MeC_6H_4	**3a**	Ar = 4-MeC_6H_4	88
2	**1b**	Ar = 4-$MeOC_6H_4$	**3b**	Ar = 4-$MeOC_6H_4$	80
3	**1c**	Ar = 4-$NO_2C_6H_4$	**3c**	Ar = 4-$NO_2C_6H_4$	50
4	**1d**		**3d**		84
5	**1e**		**3e**		88
6	**1f**		**3f**		77
7	**1g**		**3g**		71 (d.r. 90:10)
8	**1h**		**3h**		67 (d.r. 70:30)
9	**1i**		**3i**		57
10	**1j**		**3j**		84
11	**1k**		**3k**		88
12	**1l**		**3l**		89
					
13	**1m**	Ar = 4-$NO_2C_6H_4$	**3m**	Ar = 4-$NO_2C_6H_4$	62[c]

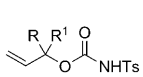
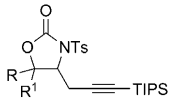
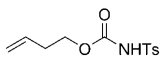
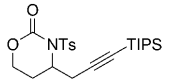
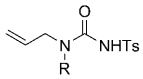
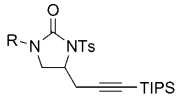
[a] Reaction conditions: 0.40 mmol of **1**, 0.040 mmol of $PdCl_2$, 0.48 mmol of TIPS-EBX (**2a**), 1.44 mmol of LiCl in 10 mL of EtOH, 2–5 h, RT. [b] Yield after purification by column chromatography. [c] 0.40 mmol of **1**, 0.040 mmol of $[Pd(hfacac)_2]$, 0.48 mmol of TIPS-EBX (**2a**), 0.48 mmol of 4-chlorosalicylic acid in 10 mL of CH_2Cl_2, 15 h, RT.

was required, as no product was obtained using alkynyl halides or alkynyliodonium salts. The smaller TMS group gave a lower yield (Table 1, entry 8), but the introduction of a phenyl group led to 58% yield (Table 1, entry 9).[13]

The scope of the reaction was then examined (Table 2). Modification of the benzenesulfonyl group showed that tosyl amide **1a** was optimal (Table 2, entry 1). 4-Methoxybenzenesulfonyl amide **1b** gave a similar yield (Table 2, entry 2). The lactam was obtained in 50% yield with the easily removable nosyl group (Table 2, entry 3). Good results were obtained for the synthesis of nitrogen-protected 5-propargyl pyrrolidinones (Table 2, entries 4–8). The reaction was tolerant to substitution α to the carbonyl group (Table 2, entries 4–6), thus allowing facile access to azaspiro compounds (Table 2, entries 5 and 6). Substitution at the allylic position with a phenyl group gave the *trans* product in 71% yield and 90:10 d.r. (Table 2, entry 7). The reaction was also successful for the synthesis of bicyclic heterocycle **3h** (Table 2, entry 8). Cyclization reactions to give six-membered rings are usually more challenging. Nevertheless, simple *N*-tosyl 5-hexenamide gave propargyl piperidone **3i** in 57% yield (Table 2, entry 9). The yield increased for more rigid substrates (Table 2, entries 10–12). Arylpiperazines derived from pyrroles or indoles are key structural elements in bioactive compounds.[14] We then examined substitution on the double bond. Although no reactivity was observed with vicinally disubstituted olefins, the cyclized product could be isolated in 62% yield with geminally disubstituted alkene **1m** under modified reaction conditions (Table 2, entry 13). This result is promising, because it indicates that the reaction could be extended to substituted olefins after adequate optimization.

As our protocol was successful for the synthesis of lactams, we wondered if a second heteroatom would be tolerated. We concentrated first on *O*-allyl and homoallyl carbamates (Table 3, entries 1–4). Allyl tosylcarbamate **6a** was converted into the corresponding 4-propargyl oxazolidinone **7a** in 83% yield (Table 3, entry 1). Substitution at the allylic position was also tolerated (Table 3, entries 2 and 3), although the diastereoselectivity was lower than for *N*-tosyl pentenamides. Homoallyl tosylcarbamate **6d** afforded the six-membered ring product in 59% yield (Table 3, entry 4). Finally, we studied the behavior of allyl ureas under our

Table 3: Aminoalkynylation of activated carbamates and ureas.[a]

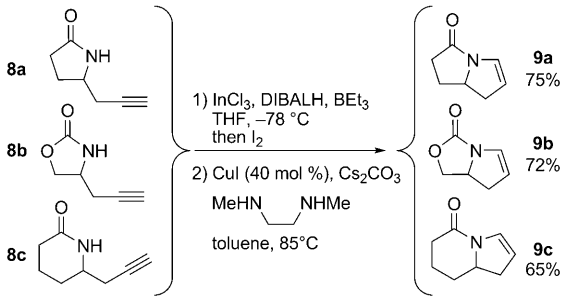
Entry	Substrate		Product		Yield [%][b]
					
1	**6a**	R = H, R^1 = H	**7a**	R = H, R^1 = H	83
2	**6b**	R = Me, R^1 = H	**7b**	R = Me, R$^{1\prime}$ = H	66 (d.r. 61:39)
3	**6c**	R = Cy, R^1 = H	**7c**	R = Cy, R^1 = H	58 (d.r. 66:34)
4	**6d**		**7d**		59
					
5	**6e**	R = H	**7e**	R = H	79
6	**6f**	R = allyl	**7f**	R = allyl	67
7	**6g**	R = Bn	**7g**	R = Bn	65

[a] Reaction conditions: 0.40 mmol of **6**, 0.040 mmol of $PdCl_2$, 0.48 mmol of TIPS-EBX (**2a**), 1.44 mmol of LiCl in 10 mL of EtOH, 2–5 h, RT. [b] Yield after purification by column chromatography. Bn = benzyl, Cy = cyclohexyl.

optimal reaction conditions (Table 3, entries 5–7). Control of O versus N cyclization is more difficult for urea, owing to the enhanced nucleophilicity of the oxygen atom. Nevertheless, only propargyl imidazolidinones were isolated in 65–79% yields when using either free or allyl- and benzyl-protected ureas.

As several new bonds are formed during the reaction, understanding the mechanism is challenging. Complete conversion of the hypervalent iodine reagent (TIPS-EBX) into 2-iodobenzoic acid and the dimerized acetylene was observed by ^{1}H NMR spectroscopy when it was mixed with a stoichiometric amount of $Li_2[PdCl_4]$. A shift of the olefin and aliphatic signals was observed in the ^{1}H NMR spectrum of the *N*-tosyl amide **1a** when added to a stoichiometric amount of the catalyst.[15] The addition of TIPS-EBX (**2a**) to this mixture then resulted in rapid formation of the product. These preliminary results seem to indicate that an initial aminopalladation and subsequent oxidative alkynylation could be envisaged. Further investigation is obviously required to elucidate the mechanism.

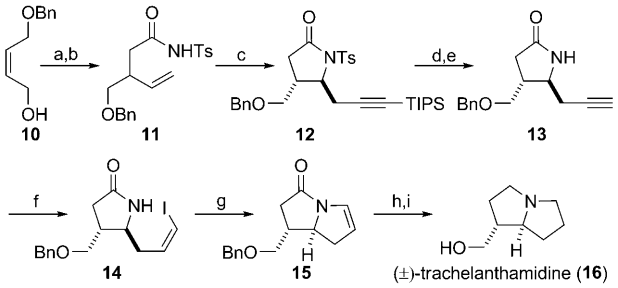
At this point, we turned our attention to the second cyclization step required to access pyrrolizidine and indolizidine heterocycles. Removal of the tosyl group from **3a** could be performed in 97% yield by treatment with [Li(naphthalenide)]. The desilylation of the triple bond was then accomplished with TBAF to give 87% yield. Cyclization of pyrrolizidinone **8a** was then examined (Scheme 2). As no product was obtained using ruthenium-catalyzed methods reported for the intermolecular hydroamination of alkynes with amides,[6b,c] we investigated a two-step approach via a vinyl iodide intermediate. Hydroindiation of the acetylene with $HInCl_2$ and subsequent quenching with iodine gave the



Scheme 2. Cyclization to form bicyclic heterocycles. The scheme shows individual reactions under the same conditions (i.e. **8a**→**9a**, **8b**→**9b**, **8c**→**9c**). DIBALH = diisobutylaluminum hydride, THF = tetrahydrofuran.

(*Z*)-vinyl iodide in 99% yield (*Z*/*E* 15:1).[8] This is the first example of the use of Oshima's method in the presence of an amide group and demonstrates the strength of this underutilized protocol. The conditions described by Buchwald for the intermolecular vinylation of amides gave pyrrolizidine **9a** in 75% yield.[7c,d] The same procedure could be successfully applied to the cyclization of oxazolidinone **8b** and indolizidinone **8c** in 72% and 65% overall yields, respectively.

Our strategy was then applied to the synthesis of the pyrrolizidine alkaloid (±)-trachelanthamidine (**16**; Scheme 3).[16] Amide **11** was obtained through Johnson–Claisen rearrangement of protected butene diol **10**,[17] subsequent hydrolysis, and treatment with *p*-tosylisocyanate. The aminoalkynylation of tosyl amide **11** proceeded in 72% yield and 83:17 dr. The tosyl and silyl groups were removed and cyclization on the triple bond proceeded in 69% overall yield. Separation of the two diastereoisomers was achieved after cyclization. Reduction of the enamide and debenzylation of the alcohol were achieved in quantitative yield. Finally, reduction of the amide group using $LiAlH_4$ gave racemic trachelanthamidine (**16**) in nine steps and 22% overall yield from **10**.



Scheme 3. Total synthesis of (±)-trachelanthamidine (**16**). Reaction conditions: a) $CH_3C(OEt)_3$, $EtCO_2H$, 100°C to 160°C; then KOH, MeOH, reflux, 80%; b) *p*-TsNCO, Et_3N, THF, RT, 80%; c) 5 mol% of $PdCl_2$, LiCl, TIPS-EBX (**2a**), EtOH, RT, 72%; 83:17 d.r.; d) Li/naphthalene, THF, −78°C, 77%; e) TBAF, THF, 0°C to RT, 98%; f) 1) $InCl_3$, DIBALH, 2) Et_3B, 3) I_2, THF, −50°C, 95%; g) 40 mol% CuI, Cs_2CO_3, *N*,*N*′-dimethylethylenediamine, toluene, 85°C, 73%; h) H_2, Pd/C, MeOH, RT, quantitative; i) $LiAlH_4$, THF, reflux, 94%. TBAF = tetra-*n*-butylammonium fluoride.

In summary, a novel strategy for the synthesis of nitrogen-bridged bicyclic heterocycles has been reported. The palladium-catalyzed intramolecular aminoalkynylation of terminal olefins was operationally simple and could be successfully applied to tosyl amides, carbamates, and ureas. Both five- and six-membered rings were obtained in good to excellent yields. After facile removal of protecting groups, iodination of the triple bond, and subsequent copper-catalyzed vinylation of the amide gave access to the core of pyrrolizidine and indolizidine heterocycles and led to a new total synthesis of (±)-trachelanthamidine (**16**). Further work towards the elucidation of the reaction mechanism and the development of an asymmetric version of the transformation are ongoing.

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[1] a) J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773; b) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191.
[2] T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795.
[3] For a few selected references, see: a) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800; b) S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem.* **2002**, *114*, 172; *Angew. Chem. Int. Ed.* **2002**, *41*, 164; c) R. I. McDonald, S. S. Stahl, *Angew. Chem.* **2010**, *122*, 5661; *Angew. Chem. Int. Ed.* **2010**, *49*, 5529; d) R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 17778.
[4] Aminocarbonylation: a) Y. Tamaru, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1988**, *53*, 5731; b) T. A. Cernak, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 3124; aminooxygenation: c) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690; d) L. V. Desai, M. S. Sanford, *Angew. Chem.* **2007**, *119*, 5839; *Angew. Chem. Int. Ed.* **2007**, *46*, 5737; e) P. H. Fuller, J. W. Kim, S. R. Chemler, *J. Am. Chem. Soc.* **2008**, *130*, 17638; f) H. M. Lovick, F. E. Michael, *J. Am. Chem. Soc.* **2010**, *132*, 1249; g) T. de Haro, C. Nevado, *Angew. Chem.* **2011**, *123*, 936; *Angew. Chem. Int. Ed.* **2011**, *50*, 906; diamination: h) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; i) J. Streuff, C. H. Hovelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; j) K. Muñiz, *J. Am. Chem. Soc.* **2007**, *129*, 14542; k) K. Muñiz, C. H. Hovelmann, J. Streuff, *J. Am. Chem. Soc.* **2008**, *130*, 763; l) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 15945; arylamination: m) J. E. Ney, J. P. Wolfe, *Angew. Chem.* **2004**, *116*, 3689; *Angew. Chem. Int. Ed.* **2004**, *43*, 3605; n) J. P. Wolfe, *Synlett* **2008**, 2913; o) J. D. Neukom, N. S. Perch, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 6276; p) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488; q) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, F. D. Toste, *Angew. Chem.* **2010**, *122*, 5651; *Angew. Chem. Int. Ed.* **2010**, *49*, 5519; r) G. Z. Zhang, L. Cui, Y. Z. Wang, L. M. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474; others: s) A. W. Lei, X. Y. Lu, G. S. Liu, *Tetrahedron Lett.* **2004**, *45*, 1785; t) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618; u) F. E. Michael, P. A. Sibbald, B. M. Cochran, *Org. Lett.* **2008**, *10*, 793; reviews: v) A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142; w) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318.
[5] S. Nicolai, S. Erard, D. Fernández González, J. Waser, *Org. Lett.* **2010**, *12*, 384.
[6] a) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4253; b) L. J. Goossen, J. E. Rauhaus, G. J. Deng, *Angew. Chem.* **2005**, *117*, 4110; *Angew. Chem. Int. Ed.* **2005**, *44*, 4042; c) L. J. Goossen, K. S. M. Salih, M. Blanchot, *Angew. Chem.* **2008**, *120*, 8620; *Angew. Chem. Int. Ed.* **2008**, *47*, 8492.
[7] a) Y. Kozawa, M. Mori, *Tetrahedron Lett.* **2002**, *43*, 111; b) Y. Kozawa, M. Mori, *J. Org. Chem.* **2003**, *68*, 3064; c) L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667; d) L. L. W. Cheung, A. Yudin, *Org. Lett.* **2009**, *11*, 1281.
[8] K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2002**, *4*, 2993.
[9] The exceptional properties of ethynyl benziodoxolone reagents were key for success; a) M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 5511; b) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 654; c) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem.* **2009**, *121*, 9510; *Angew. Chem. Int. Ed.* **2009**, *48*, 9346; d) D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457; e) J. P. Brand, J. Waser, *Angew. Chem.* **2010**, *122*, 7462; *Angew. Chem. Int. Ed.* **2010**, *49*, 7304; For reviews, see: f) T. Wirth, *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*, *Vol. 224*, Springer, New York, **2003**; g) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; h) J. P. Brand, D. Fernández González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102.
[10] See the Supporting Information for a complete list of tested reaction conditions.
[11] The in situ generation of $Li_2[PdCl_4]$ from cheaper $PdCl_2$ and LiCl was still preferred for preparative reactions. Other metal additives, such as CuI, were not successful, either with hypervalent iodine reagents or alkynyl halides (See Table S3 and S4 in the Supporting Information).
[12] a) K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26; *Angew. Chem. Int. Ed.* **2002**, *41*, 26; b) X. Y. Lu, *Top. Catal.* **2005**, *35*, 73.
[13] This result is interesting in terms of further extension of the scope of the reaction. Nevertheless, we decided to focus first on the use of TIPS-EBX (**2a**), as the protecting groups of the silyl acetylenes obtained were easily removed.
[14] a) J. L. Mokrosz, B. Duszynska, M. H. Paluchowska, *Arch. Pharm.* **1994**, *327*, 529; b) S. Butini et al., *J. Med. Chem.* **2009**, *52*, 151. See the Supporting Information for full citation.
[15] See Figures S1 and S2. Investigations are ongoing to identify the intermediate that is formed.
[16] a) G. P. Menschikov, *Zh. Obshch. Khim.* **1946**, *16*, 1311; b) S. Danishefsky, R. McKee, R. K. Singh, *J. Am. Chem. Soc.* **1977**, *99*, 4783; c) H. Ishibashi, M. Sasaki, T. Taniguchi, *Tetrahedron* **2008**, *64*, 7771.
[17] S. Couty, C. Meyer, J. Cossy, *Tetrahedron* **2009**, *65*, 1809.

