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Two Titanium-Catalyzed Reaction Sequences for Syntheses of Pyrroles from (*E*/*Z*)-Chloroenynes or α-Haloalkynols

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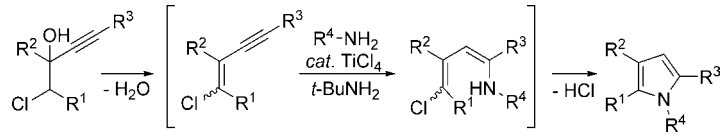
ABSTRACT



Titanium-catalyzed intermolecular hydroaminations of (*E*/*Z*)-chloroenynes enabled an efficient pyrrole synthesis, which set the stage for the development of a user-friendly one-pot reaction for the regioselective preparation of fully substituted pyrroles from easily accessible α-haloalkynols.

Regioselectively substituted pyrroles represent indispensable structural motifs of among other biologically active natural products or molecular sensors.[1] Therefore, a continued strong demand exists for flexible syntheses of this five-membered heterocycle.[2] Transition-metal-catalyzed[3] C−N bond-forming reactions have proven highly useful for the preparation of nitrogen-containing compounds[4] in both academia as well as pharmaceutical industries.[5,6] In particular, protocols relying on addition reactions of *N*-nucleophiles onto alkynes set the stage for the development of synthetically useful approaches.[7] In a recent example, Buchwald and co-workers reported on an elegant application of catalytic C−N coupling/hydroamidation sequences[8] to the synthesis of substituted pyrroles, employing haloenynes as starting materials.[9] This copper-catalyzed transformation consisted of an initial intermolecular alkenylation of $BocNH_2$, along with a subsequent intramolecular hydroamidation. Unfortunately, this reaction was thus restricted to the use of diastereomerically pure (*Z*)-iodo- or (*Z*)-bromoenynes as well as of the less basic *N*-nucleophile $BocNH_2$.

(1) For selected reviews, see: (a) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256. (b) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (c) Fuerstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603. (d) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753–1783. (e) Novak, P.; Mueller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207–281.

(2) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.; Oxford, 2000.

(3) (a) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004.

(4) For selected representative examples of transition-metal-catalyzed pyrrole syntheses, see: (a) Fontaine, P.; Masson, G; Zhu, Y. *Org. Lett.* **2009**, *74*, 1555–1558. (b) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 129–134. (c) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem.—Eur. J.* **2009**, *15*, 227–236. (d) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452. (e) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. (f) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510–1513. (g) Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382. (h) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813. (i) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169–1171. (j) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151–2153. (k) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261. (l) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664–5667. (m) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (n) Braun, R. U.; Zeitler, K.; Mueller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3300. (o) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074–2075. (p) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277–4278, and references cited therein.

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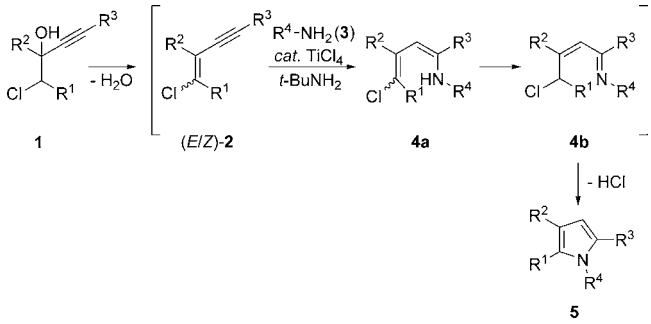
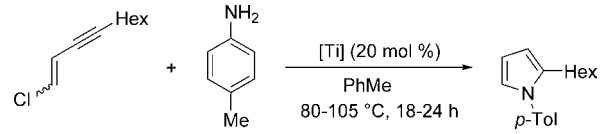
Scheme 1. Titanium-Catalyzed Pyrrole Synthesis



On the contrary, we wondered whether a complementary approach could be initiated through a catalytic intermolecular hydroamination of haloenynes **2** (Scheme 1). This should enable a cyclization, proceeding through a [1,5]H sigmatropic shift, in essence a tautomerization, followed by an intramolecular nucleophilic substitution.[10] Therefore, it should be possible to employ diastereomers (*E*)-**2**, or even, often more broadly available, mixtures of diastereomers (*E*/*Z*)-**2**. Herein, we show that the envisioned strategy could be realized with inexpensive titanium hydroamination catalysts,[11,12] which allowed for the use of more basic amines as well as of chloro-substituted enynes (*E*/*Z*)-**2**. Furthermore, we disclose a user-friendly one-pot synthesis of highly substituted pyrroles starting from easy to prepare α-haloalkynols.

At the outset of our studies, we probed our previously developed catalytic system consisting of inexpensive $TiCl_4$ and *t*-$BuNH_2$[13,14] for the synthesis of pyrrole **5a** (Table 1). Gratifyingly, both diastereomers (*Z*)-**2a** and (*E*)-**2a**, as well as their mixtures (*E*/*Z*)-**2a**, provided comparable yields of desired product **5a** (entries 1−3). Furthermore, the additive

Table 1. Titanium-Catalyzed Pyrrole Synthesis[a]



2a **3a** **5a**

entry	**2a** diastereomer	[Ti]	*T* (°C)	yield (%)
1	*Z*	$TiCl_4$/*t*-$BuNH_2$	105	80
2	*E*	$TiCl_4$/*t*-$BuNH_2$	105	83
3	*E*/*Z*	$TiCl_4$/*t*-$BuNH_2$	105	86
4	*E*/*Z*	$TiCl_4$	105	22
5	*E*/*Z*	$Ti(NMe_2)_4$	105	82
6	*E*/*Z*		105	
7	*E*/*Z*	$TiCl_4$/*t*-$BuNH_2$	80	84
8	*E*/*Z*	$TiCl_4$/*t*-$BuNH_2$	25	

[a] Reaction conditions: **2a** (1.00 mmol), **3a** (1.25 mmol), [Ti] (20 mol %), *t*-$BuNH_2$ (1.20 mmol), PhMe (2.0 mL), 18−24 h; yields of isolated product.

t-$BuNH_2$ was found to be essential for achieving satisfactory yields (entry 4). While $Ti(NMe_2)_4$[15] served as an effective alternative as well (entry 5), a titanium hydroamination catalyst turned out to be mandatory (entry 6). Notably, a lower reaction temperature of 80 °C gave rise to a synthetically useful yield of pyrrole **5a** (entry 7). On the contrary, a conversion of the starting materials did not occur at ambient temperature (entry 8).

With an effective catalytic system in hand, we explored its scope and limitations in the one-pot pyrrole synthesis (Table 2). A variety of (*E*/*Z*)-chloroenynes **2** were converted with anilines **3** in high yields (entries 1−4). However, an aryl-substituted alkyne gave a lower regioselectivity in the intermolecular hydroamination,[13b] which led to a less satisfactory result (entry 5). Anilines displaying different halides as functional groups, including 2-iodoaniline (**3h**), were chemoselectively transformed into the desired indoles **5g**−**5k** (entries 6−10), a valuable asset for further catalytic functionalization chemistry. In addition, alkyl amines **3i** and **3j** could be employed as substrates as well, thereby delivering pyrroles **5l** and **5m**, respectively (entries 11 and 12).

Since haloenynes **2** are often tedious to prepare, we desired to establish a more user-friendly approach, exploiting easily accessible starting materials. Therefore, we turned our attention to the use of α-haloalkynols **1**, which are available through nucleophilic addition reactions of acetylides to

(5) (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309.

(6) (a) Schlummer, B.; Scholz, U. In *Modern Arylation Methods*; Ackermann, L., Ed.; Weinheim, 2009; pp 69−127. (b) Scholz, U. In *Amino Group Chemistry*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 333−375. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23–39.

(7) Selected reviews on hydroamination reactions: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (b) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382–5391. (c) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398. (e) Duncan, A. P.; Bergman, R. G. *Chem. Rec.* **2002**, *2*, 431–445.

(8) For related regioselective indole syntheses making use of C−N coupling/hydroamination sequences, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 439–442. (b) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311–11316. (c) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Perez, A.; Fananas, F. J. *J. Org. Chem.* **2007**, *72*, 5113–5118, and references cited therein.

(9) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079–7082.

(10) Alternatively, an addition/elimination mechanism could be operative. The feasibility of the proposed [1,5]H sigmatropic shift through reactions with isotopically labeled compounds was thus far not probed.

(11) For titanium-catalyzed hydroamination reactions for pyrrole syntheses, see: (a) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957–2960. (b) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541–9544. (c) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459–5460.

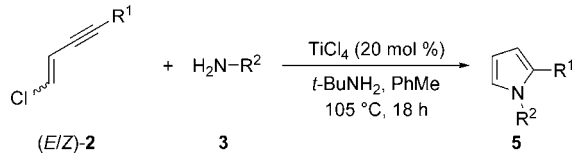
(12) For selected reviews on titanium-catalyzed hydroaminations, see: (a) Odom, A. L. *Dalton Trans.* **2005**, 225–233. (b) Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2243–2255, and references cited therein.

(13) For examples of this system for catalytic hydroaminations, see: (a) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2008**, *64*, 769–777. (b) Ackermann, L.; Kaspar, L. T. *J. Org. Chem.* **2007**, *72*, 6149–6153. (c) Ackermann, L.; Kaspar, L. T.; Althammer, A. *Org. Biomol. Chem.* **2007**, *5*, 1975–1978. (d) Abbiati, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839–4842. (e) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824–2825. (f) Ackermann, L. *Organometallics* **2003**, *22*, 4367–4368.

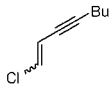
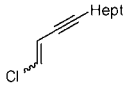
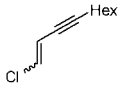
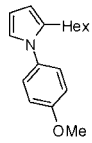
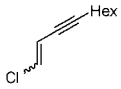
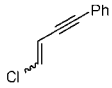
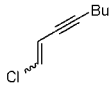
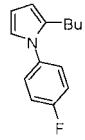
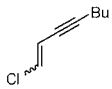
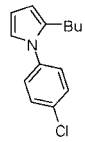
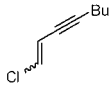
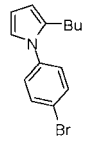
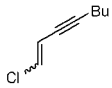
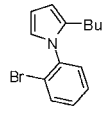
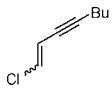
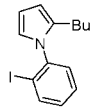
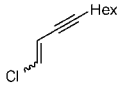
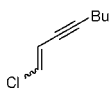
(14) A review: Ackermann, L. *Synlett* **2007**, 507–526.

(15) For representative examples of catalytic hydroaminations with $Ti(NMe_2)_4$, see: (a) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956–11963. (b) Ackermann, L.; Bergman, R. G. *Org. Lett.* **2002**, *4*, 1475–1478. (c) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967–3969.

Table 2. Scope of Titanium-Catalyzed Pyrrole Synthesis[a]

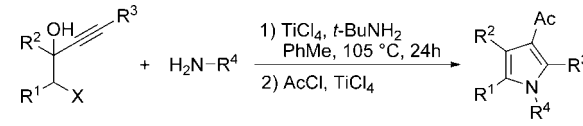


(*E*/*Z*)-**2** **3** **5**

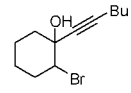
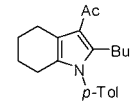
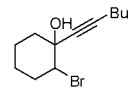
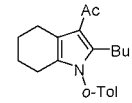
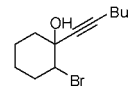
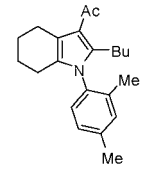
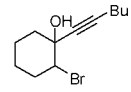
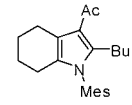
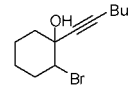
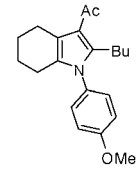
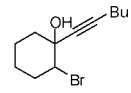
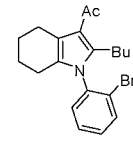
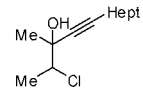
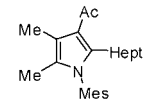
entry	**2**	R^2	**5**		yield
1		*p*-Tol **3a**		**5b**	86%
2		*p*-Tol **3a**		**5c**	68%
3		4-MeOC$_6$H$_4$ **3b**		**5d**	71%
4		Mes **3c**		**5e**	84%
5		Mes **3c**		**5f**	39%[b]
6		4-FC$_6$H$_4$ **3d**		**5g**	77%
7		4-ClC$_6$H$_4$ **3e**		**5h**	79%
8		4-BrC$_6$H$_4$ **3f**		**5i**	76%
9		2-BrC$_6$H$_4$ **3g**		**5j**	63%
10		2-IC$_6$H$_4$ **3h**		**5k**	60%
11		Cy **3i**		**5l**	52%[b]
12		MesCH$_2$ **3j**		**5m**	87%

[a] Reaction conditions: (*E*/*Z*)-**2** (1.00 mmol), **3** (1.25 mmol), $TiCl_4$ (20 mol %), *t*-$BuNH_2$ (1.20 mmol), PhMe (2.0 mL), 105 °C, 18 h; yields of isolated product. [b] GC analysis.

Table 3. Regioselective Titanium-Mediated Synthesis of Fully-Substituted Pyrroles **5**[a]



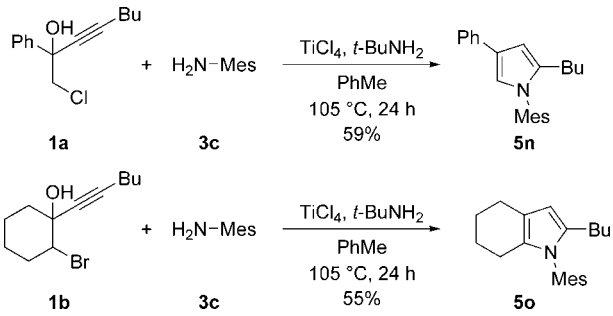
1 **3** **5**

entry	**1**	R^4	**5**		yield
1		*p*-Tol **3a**		**5p**	51%
2		*o*-Tol **3k**		**5q**	57%
3		2,4-Me$_2$C$_6$H$_3$ **3l**		**5r**	64%
4		Mes **3c**		**5s**	81%
5		4-MeOC$_6$H$_4$ **3b**		**5t**	51%
6		2-BrC$_6$H$_4$ **3g**		**5u**	59%
7		Mes **3c**		**5v**	65%
8		2-FC$_6$H$_4$ **3m**		**5w**	49%
9		Mes **3c**		**5x**	61%

[a] Reaction conditions: (a) **1** (1.00 mmol), **3** (1.25 mmol), $TiCl_4$ (1.20 mmol), *t*-$BuNH_2$ (7.20 mmol), PhMe (2−6 mL), 105 °C, 24 h; (b) AcCl, $TiCl_4$ (2.00 mmol), 0−23 °C; yields of isolated product.

α-halo ketones. Satisfyingly, inexpensive $TiCl_4$ could be employed here both as a dehydrating reagent as well as to ensure the hydroamination reaction, enabling the formation of tri- or tetrasubstituted pyrroles **5n** and **5o** (Scheme 2).

Scheme 2. Hydroamination-Based Sequence for the Regioselective Synthesis of Pyrroles **5n** and **5o**



Finally, we probed the regioselective synthesis of fully decorated pentasubstituted pyrroles. Hence, we functionalized the remaining C−H bonds of the pyrrole moieties through electrophilic aromatic substitution reactions within a one-pot protocol (Table 3). Various annulated pyrroles were prepared in high yields (entries 1−5), as was product **5u** bearing a valuable halo substituent (entry 6). The transformation was not restricted to the use of cyclic starting materials **1** but allowed also for the preparation of nonannulated pyrroles **5v**−**5x** (entries 7−9).

In conclusion, we developed efficient pyrrole syntheses relying on titanium-catalyzed intermolecular hydroamination reactions of diastereomeric mixtures of chloroenynes. Thus, we described the use of α-haloalkynols for a pyrrole synthesis through a reaction sequence comprising (a) a dehydration, (b) an intermolecular hydroamination, (c) a [1,5]H sigmatropic shift, and (d) an intramolecular nucleophilic substitution. With these two methodologies in hand, a variety of di-, tri-, tetra-, and pentasubstituted pyrroles proved to be accessible in a highly modular, yet regioselective, fashion.

Acknowledgment. Support by the DFG is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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