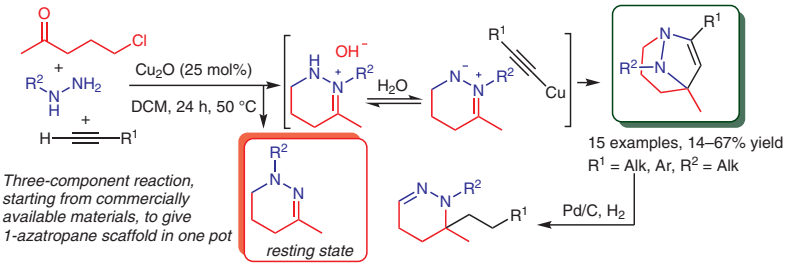
Synlett W. E. Van Beek et al. Letter

Synthesis of 1-Aza-6,7-dehydrotropanes via Copper(I)-Catalyzed Coupling of 5-Chloropentan-2-one with Hydrazines and Terminal Alkynes

Wim E. Van Beek[a]
Karel Weemaes[a]
Wouter A. Herrebout[b]
Christophe M. L. Vande Velde[c]
Kourosch Abbaspour Tehrani*[a]

[a] Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
Kourosch.AbbaspourTehrani@uantwerpen.be
[b] Research group Molecular Spectroscopy, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
[c] Faculty of Applied Engineering, Advanced Reactor Technology, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium

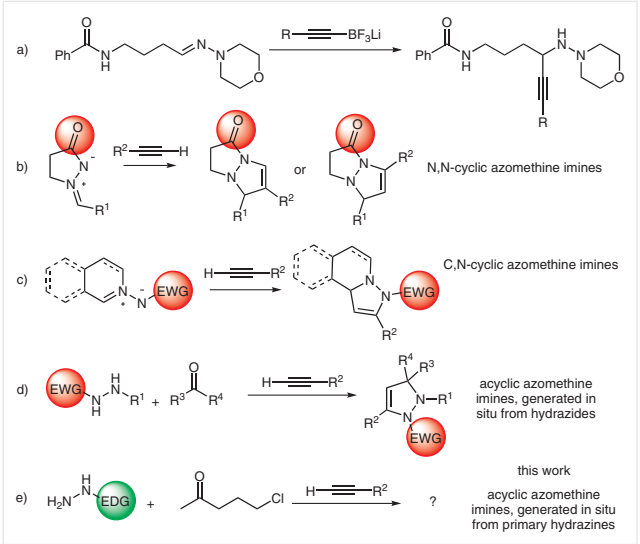


Received: 23.08.2018
Accepted after revision: 25.09.2018
Published online: 24.10.2018
DOI: 10.1055/s-0037-1611041; Art ID: st-2018-k0544-l

Abstract A one-pot, three-component, Cu(I)-catalyzed coupling of primary hydrazines, 5-chloropentan-2-one, and terminal alkynes was developed. The resulting 1-aza-6,7-dehydrotropanes compose a new class of substances while related 1-azatropanes are scarcely described in literature and closely resemble tropane alkaloids. Hydrogenation of the double bond in 1-aza-6,7-dehydrotropanes triggered a rearrangement, involving a [1,3]-hydride shift, forming cyclic hydrazones.

Key words multicomponent reactions, alkynes, hydrazines, ketones, copper catalysis, 1-azatropanes

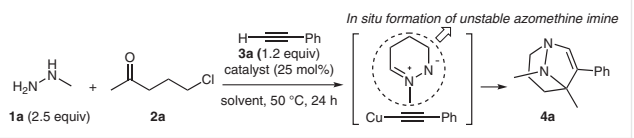
Alkynylation of hydrazones is, compared to alkynylation of imines, an underexplored research topic due to the intrinsic low electrophilicity of hydrazones. To the best of our knowledge, there has only been one example of direct alkynylation of hydrazones reported to date (Scheme 1, a).[1] Alkynylation could in this case be accomplished by using *n*-BuLi to form *in situ* the lithium alkynyl trifluoroborate. Often, products of alkynylation of hydrazones are subject to intramolecular hydrohydrazination reactions, generating (annulated) pyrazoline derivatives.[2] However, these products could also arise from [3+2] cycloaddition of azomethine imines, generated from hydrazones and alkynes. Many examples of [3+2] cycloadditions of azomethine imines and alkynes exist, and generally azomethine imines need to be formed in a separate step. Stable azomethine imines are easily made from hydrazides, i.e., hydrazines possessing an electron-withdrawing carbonyl moiety, and aldehydes or ketones, and can be divided into different categories: *C,N*-cyclic,[2d,e,3] *N,N*-cyclic,[2a,4] and acyclic azomethine imines[2b,c] (Scheme 1, b–d).[5] Other azomethine imines, generated from hydrazines, are generally unstable and can only be formed *in situ*.[2b,c] Recently, we reported a three-component coupling of ω-halogenated ketones, primary amines, and terminal alkynes, where a cyclic iminium species was found to possess enhanced electrophilic properties.[6] We were curious whether a cyclic hydrazonium or azomethine imine species would likewise exhibit similar enhanced electrophilic properties or special reactivity.



Scheme 1 a) Alkynylation on hydrazone; b) to d) previously reported [3+2] cycloadditions of different azomethine imines and alkynes; e) our approach.

Downloaded by: University of Western Ontario. Copyrighted material.

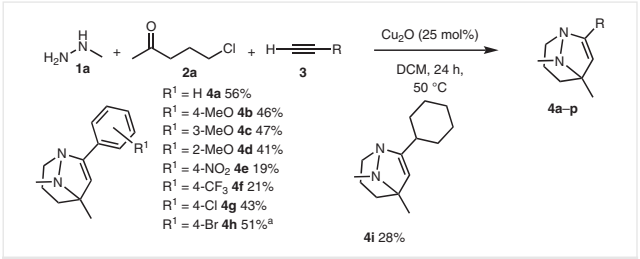
An initial trial experiment using methylhydrazine (**1a**), 5-chloropentan-2-one (**2a**), and phenylacetylene (**3a**) under Cu_2O catalysis (25 mol%) in acetonitrile at 50 °C for 24 hours yielded a single product **4a** in a moderate 35% yield (Scheme 2).



Scheme 2 Metal-catalyzed three-component coupling of methylhydrazine, 5-chloropentan-2-one, and phenylacetylene leads to the formation of 1-aza-6,7-dehydrotropane **4a**

A number of different transition-metal catalysts was evaluated and this revealed the superior catalytic activity of Cu(I) salts over, among others, Fe(III), Ag(I), Au(I), Zn(II), and Cu(II) salts (see Supporting Information – Table S1), with copper(I) oxide as the best catalyst. Interestingly, the choice of metal catalyst counterion was previously found to be important, due to the possibility of protonation of the counterion leading to formation of an acid that could catalyze the dimerization of azomethine imines.[2c] Other Cu(I) salts such as the acetate, chloride, or triflate all gave similar results as the oxide. With regard to the pK_a an improvement could be expected from triflic acid to hydrochloric acid, acetic acid, and water, but in fact CuOTf, surprisingly, gave a slightly better yield of 41% in comparison to Cu_2O (35%). Since one equivalent of HCl is already formed by the ring closure of the starting material, most likely the role of the counterion is not of much importance here, and therefore Cu_2O was selected as the catalyst of choice. A number of solvents was evaluated (see Supporting Information – Table S2). Generally, polar and apolar solvents gave low yields, while intermediately polar solvents such as chlorinated solvents dichloromethane (DCM), 1,2-dichloroethane, and chloroform gave the best yields. Dichloromethane as solvent gave the best result, with an associated 58% NMR yield. Prolongation of reaction times and higher reaction temperatures did not lead to higher yields. The low screening yield can be explained by the formation of cyclic hydrazone side product (*cf.* Scheme 6).

Next, we investigated the scope of the reaction with regard to the alkyne component (Scheme 3).[7] A number of substituted terminal aryl alkynes were evaluated. Electron-donating groups were tolerated well (**4b–d**), but strong electron-withdrawing groups such as 4-nitro or 4-trifluoromethyl gave only low yields of products **4e–f**, while weak electron-withdrawing 4-chloro or 4-bromo gave similar yields of **4g** and **4h** as nonsubstituted phenylacetylene **4a**. The presence of heteroatoms such as nitrogen in 2-pyridinylacetylene and oxygen in methyl propiolate or 1-phenylprop-2-yn-1-ol rendered the alkyne less nucleophilic and completely blocked the reaction as no reaction products **4** were observed. The absence of reaction products **4** could in these cases also be explained by additional complexation of the Cu(I) ion with the heteroatom rendering the alkyne less nucleophilic. An aliphatic acetylene, such as cyclohexylacetylene, generates the product **4i** in a low yield of 28%, but illustrates that the reaction is still possible. Conducting the reaction with an internal alkyne such as dimethyl acetylenedicarboxylate (DMAD), a popular dipolarophile in [3+2] cycloadditions, did not lead to any [3+2]-cycloaddition product **4**. Although DMAD is a very good dipolarophile for [3+2] cycloadditions, it is not capable of forming a copper acetylide species, since it does not possess a terminal C(sp)–H proton. In a similar way, the use of 1-propynylbenzene, closely resembling phenylacetylene but lacking a terminal C(sp)–H proton, did not lead to any coupling product **4**. Furthermore, other dipolarophiles, such as alkenes, did not lead to coupling products **4** either.



Scheme 3 Scope of the reaction regarding the alkyne.[a] 4 mmol reaction scale.

A few of the molecules **4** were solids, and example **4g** gave, after recrystallization from DCM, suitable crystals for X-ray diffraction, so that the structure of 1-azatropane **4** could be confirmed (see Figure 1 and Supporting Information – Figure S1).[8]

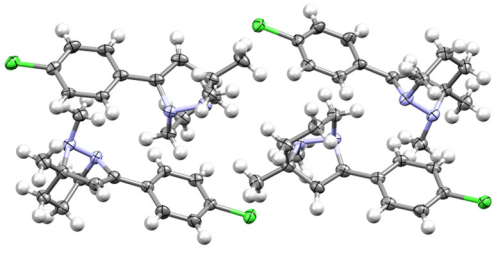


Figure 1 Crystal structure of the major disorder component of the asymmetric unit in **4g**, containing four molecules (two times two enantiomers). Displacement ellipsoids are drawn at the 50% probability level, and hydrogen atoms are drawn as spheres of arbitrary radius.

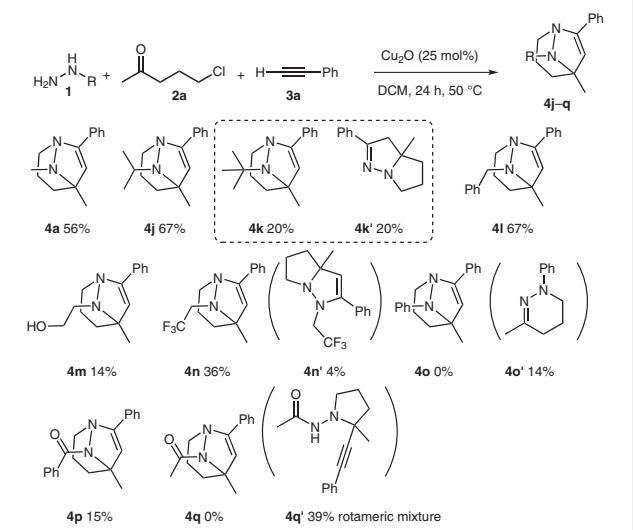
Next, the scope of hydrazines was investigated (Scheme 4). Other primary aliphatic hydrazines were evaluated; more sterically hindered isopropylhydrazine gave an improved yield of 67% of **4j**. Although the steric hindrance around the reaction center increases, the nucleophilicity of the hydrazine decreases,[9] thus resulting in more difficult formation of hydrazone side product, which is beneficial for

Downloaded by: University of Western Ontario. Copyrighted material.

the synthesis of wanted product **4j**. When the steric hindrance is increased to *tert*-butylhydrazine, the overall yield decreased to 40%, including a degradation product **4k′**. This product was not present after workup, but probably formed during column chromatography on silica. We reasoned that the slightly acidic nature of silica would prompt molecule **4k** to de-*tert*-butylate and rearrange to **4k′**.[10] To test this hypothesis, product **4k** was treated with dry trifluoroacetic acid (TFA) in DCM. After basic workup, the product was completely transformed into product **4k′** in 85% yield. Mechanistically, this rearrangement probably starts with protonation of the hydrazine moiety (by either acidic silica or TFA), followed by de-*tert*-butylation with the loss of gaseous isobutene. The presence of an N–H can now provide a loss of ring strain by rearrangement of the molecule. To our delight, the use of benzylhydrazine resulted in the formation of product **4l** in a decent 67% yield. Product **4m** was formed in a low 14% yield, indicating difficulties when hydroxyl moieties were used. When trifluoroethylhydrazine was used, product **4n** was isolated, next to a very similar isomer. High-temperature NMR spectroscopy excluded the possibility of rotamers, and a second purification attempt provided **4n** in 36% yield. The other isomer is thought to be **4n′**, since the trifluoroethyl group probably lowers the nucleophilicity of the substituted hydrazine nitrogen atom, resulting in formation of hydrazone via the unsubstituted hydrazine nitrogen atom. This assumption should be confirmed by X-ray analysis of product **4n′**, but unfortunately no suitable crystals could be grown. When phenylhydrazine was used, no reaction product **4o** was observed, but instead cyclic hydrazone **4o′** was isolated in 14% yield. The use of phenylhydrazide resulted in a sluggish 15% yield of **4p**, while the use of acethydrazide did not lead to product **4q**. Instead, 2-alkynylpyrrolidine **4q′** was isolated, which exhibited two sets of signals in the ^{13}C and ^{1}H NMR spectra. The coalescence of the signals was observed at 120 °C. These double signals are therefore believed to originate from the restricted rotation of the acetyl group around the O=C-N bond, like in DMF.[11] The use of tosylhydrazide did not lead to any intended product **4**. Disubstituted hydrazines and other ω-chloroketones did not lead to coupling products (see Supporting Information – Schemes S1 and S2).

The structure of molecules **4** is interesting as they are aza-analogues of tropane alkaloids, that are known as anticholinergic drugs, with cocaine (**5**) as one of the most famous examples (Figure 2).[12] Previous literature methods for the preparation of similar compounds describe the cycloaddition of alkenes/alkynes with diazinium betaines[13] or nucleophilic addition of *in situ* formed *N*-acylhydrazonium intermediates.[14]

In view of the limited examples of 1-azatropanes in the literature, an attempt was made to reduce the olefinic bond in the bicyclic compounds **4** by using Pd/C and hydrogen



Scheme 4 Scope of hydrazines

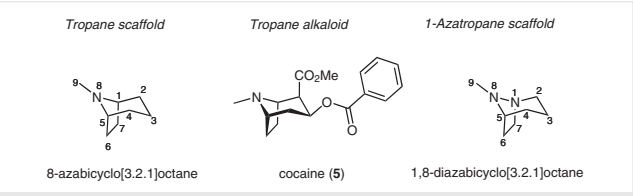
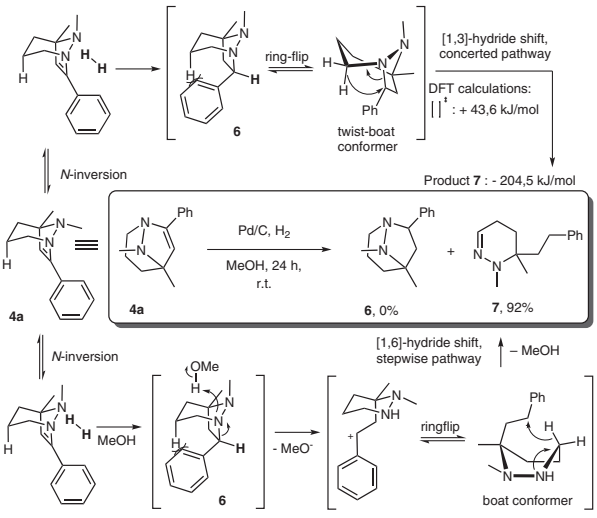


Figure 2 Tropane- and 1-azatropane scaffold, cocaine (**5**) as example

gas (Scheme 5). Product **4a** was dissolved in methanol and stirred for 24 hours at room temperature under an atmosphere of hydrogen with Pd/C. To our surprise, the hydrogenated product **6** was never observed, but hydrazone **7** was formed as the reaction product in 92% yield. Although this structure seems far-fetched at first sight, a logical explanation can be given for the formation of this reaction product. Two pathways are presented. The first pathway involves *N*-inversion, followed by *syn*-addition of hydrogen. The addition of hydrogen can only occur at one side of the double bond, since the other side is blocked by the largest ring. Molecule **6** therefore encounters strong steric hindrance, pushing the molecule into a twisted-boat conformer from where a concerted [1,3]-hydride shift might occur, forming hydrazone **7**. A second, stepwise pathway starts again with the *syn*-addition of hydrogen to molecule **4a** to create hydrogenated product **6**. The steric hindrance can, in this case, be lowered by breaking the N–C(Ph) bond, generating a secondary benzylic carbocation. Ring flip to a boat conformer allows for a [1,6]-hydride shift, eventually leading to molecule **7**. The overall process is an internal redox neutral process and is closely related to reactions were the *tert*-amino effect is invoked.[15] Similar [1,6]-hydride shifts are rare but examples exist and are generally explained by the geometry of the carbocation.[16] In order to differentiate between the two hydride shifts density functional theory

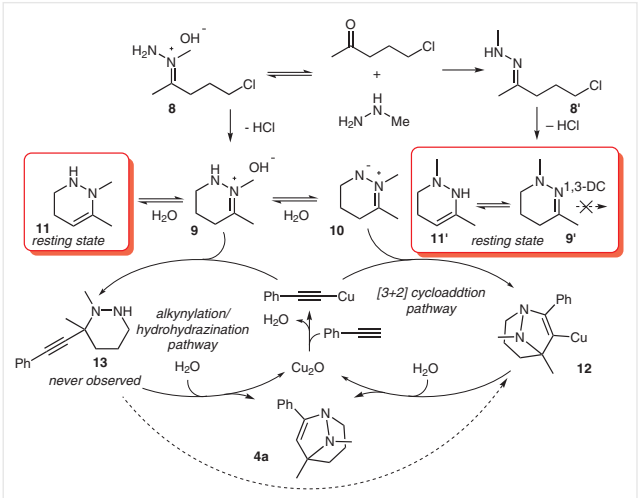
Downloaded by: University of Western Ontario. Copyrighted material.

(DFT) calculations were performed (see Supporting Information – Figure S3). These calculations support the [1,3]-hydride shift, since for the [1,6]-hydride shift no feasible carbocationic intermediate could be obtained.



Scheme 5 Hydrogenation of 1-azatropane **4a** yields a rearranged cyclic hydrazone **7**

For the synthesis of 1-aza-6,7-dihydrotropanes **4**, a reaction mechanism consisting of two possible pathways can be envisaged (Scheme 6). Both pathways start with the formation of hydrazonium salt **8** from attack of the substituted hydrazine nitrogen atom. Loss of HCl via an intramolecular substitution reaction generates cyclic hydrazonium **9**. From there azomethine imine **10** could be formed together with the tautomeric enehydrazine **11**, which can be considered as a resting state for the reaction. On the other hand, the nonsubstituted hydrazine nitrogen can react to form hydrazone **8′** which upon intramolecular substitution generates a cyclic hydrazone **9′** or enehydrazine **11′**, which are considered resting states for the reaction as they cannot undergo a 1,3-dipolar cycloaddition (1,3-DC). Independently, copper phenylacetylide is formed from copper(I) oxide with the aid of any weak base present (e.g. methylhydrazine). Copper phenylacetylide then reacts via a [3+2] cycloaddition with azomethine imine **10** to form vinyl copper species **12**, which is protonated to form target compound **4a**. Alternatively, copper phenylacetylide may react with cyclic hydrazonium **9** to form propargyl hydrazine **13**, which quickly undergoes intramolecular hydrohydrazination to form target compound **4a**. Compound **13** was, however, never observed. Propargyl hydrazine **13** could also form a π-complex with Cu^{+}, so that vinyl copper species **12** is formed, and after hydrolysis target compound **4a** can be formed. Trapping of vinyl copper species **12** was attempted with other electrophiles (see Supporting Information – Scheme S3).[4a,17] Unfortunately, this intermediate could not be trapped, probably because of the unavoidable formation of HCl as proton source in the reaction mixture.



Scheme 6 Proposed reaction mechanism

In conclusion, we developed a one-pot, three-component coupling using primary hydrazines, 5-chloropentan-2-one, and terminal alkynes that form *in situ* azomethine imines, that would otherwise be unstable. The formation of a nonhydrolyzable cyclic hydrazone side product hampers the reaction, and generally leads to moderate yields. Different substituted hydrazines could be used, but when electron-withdrawing substituents are used, the reactivity changes, as the nonsubstituted nitrogen atom preferably reacts in that case. Furthermore, different aryl- and alkyl-substituted alkynes can be coupled to generate a rare class of 1-azatropane scaffolds, which can potentially be important as aza-analogues of naturally occurring aza-tropanes.

Funding Information

This work was financed by the Agency for Innovation by Science and Technology (IWT-Flanders), the University of Antwerp (BOF), and the Hercules Foundation (project AUGE/11/029 '3D-SPACE: 3D Structural Platform Aiming for Chemical Excellence').

Acknowledgment

We thank Prof. dr. F. Lemière for HRMS measurements and Philippe Franck (Organic Synthesis, University of Antwerp) for technical assistance.

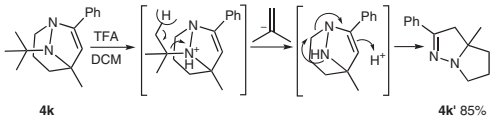
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611041.

Downloaded by: University of Western Ontario. Copyrighted material.

References and Notes

(1) Shaaban, S.; Oh, J.; Maulide, N. *Org. Lett.* **2016**, *18*, 345.
(2) (a) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049. (b) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326. (c) Hashimoto, T.; Takiguchi, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 11473. (d) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 3469. (e) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 8952.
(3) (a) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2012**, *14*, 5330. (b) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8931. (c) Chen, Z.; Ding, Q.; Yu, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 1692. (d) Harju, K.; Kylänlahti, I.; Paananen, T.; Polamo, M.; Nielsen, J.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2006**, *8*, 344.
(4) (a) Zhang, M.; Wu, F.; Wang, H.; Wua, J.; Chen, W. *Adv. Synth. Catal.* **2017**, *359*, 2768. (b) Yang, Z.-W.; Wang, J.-F.; Peng, L.-J.; You, X.-L.; Cui, H.-L. *Tetrahedron Lett.* **2016**, *57*, 5219. (c) Liu, Y.; Zhen, W.; Dai, W.; Wang, F.; Li, X. *Org. Lett.* **2013**, *15*, 874. (d) Shao, C.; Zhang, Q.; Cheng, G.; Cheng, C.; Wang, X.; Hu, Y. *Eur. J. Org. Chem.* **2013**, 6443. (e) Chen, X.; Jia, C.; Cao, L.; Zhang, D.; Liu, S.; Zhang, Q. *Chem. Res. Chin. Univ.* **2015**, *31*, 543. (f) Arai, T.; Ogino, Y.; Sato, T. *Chem. Commun.* **2013**, *49*, 7776. (g) Arai, T.; Ogino, Y. *Molecules* **2012**, *17*, 6170. (h) Yoshimura, K.; Oishi, T.; Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2011**, *17*, 3827. (i) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (j) Takamichi, O.; Kazuaki, Y.; Kazuya, Y.; Noritaka, M. *Chem. Lett.* **2010**, *39*, 1086.
(5) Schantl, J. G. *Science of Synthesis*; Thieme: Stuttgart, **2004**, Vol. 27 731.
(6) Van Beek, W. E.; Van Stappen, J.; Franck, P.; Abbaspour Tehrani, K. *Org. Lett.* **2016**, *18*, 4782.
(7) **General Experimental Procedure for the Synthesis of Products 4**
In an oven-dried microwave vessel (10 mL) were introduced Cu_2O (36 mg, 0.25 mmol), hydrazine **1** (2.5 mmol), ketone **2a** (1 mmol), alkyne **3** (1.2 mmol), and DCM (4 mL). The vessel was flushed with argon for 30 s, sealed, and introduced in a pre-heated oil bath of 50 °C and stirred during 24 h. Afterwards, the reaction mixture was poured into 0.5 N NaOH solution (20 mL) and extracted with DCM (2 × 20 mL). The organic phases were combined and dried over $MgSO_4 \cdot 3H_2O$, filtered, and evaporated *in vacuo*. The crude product was then purified by automated column chromatography on a 12 g Grace column with heptanes/EtOAc as eluting solvents.
5,8-Dimethyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (4a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2 H), 7.34–7.26 (m, 3 H), 5.78 (s, 1 H), 3.34–3.26 (m, 1 H), 2.86 (dd, 1 H, *J* = 13.3, 6.3 Hz), 2.37 (s, 3 H), 1.84–1.79 (m, 2 H), 1.48–1.43 (m, 2 H), 1.22 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 132.1, 128.5, 128.3, 126.6, 115.9, 68.8, 47.9, 37.6, 33.7, 20.0, 18.6. HRMS (ESI): *m/z* calcd for $[C_{14}H_{18}N_2 + H]^+$: 215.1543; found: 215.1542. Yellow oil, 119.4 mg (56%) isolated yield of 5,8-dimethyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**4a**) after column chromatography; R_f = 0.39 in 1:1 heptanes/EtOAc.
(8) CCDC-1846488 contains the supplementary crystallographic data for **4g**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(9) (a) Nigst, T. A.; Antipova, A.; Mayr, H. *J. Org. Chem.* **2012**, *77*, 8142. (b) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679.
(10) Mechanism for the de-*tert*-butylation and rearrangement of **4k** into **4k'** (Scheme 7)



Scheme 7

(11) Geffe, M.; Andernach, L.; Trapp, O.; Opatz, T. *Beilstein J. Org. Chem.* **2014**, *10*, 701.
(12) Grynkiewicz, G.; Gadzikowska, M. *Pharmacol. Rep.* **2008**, *60*, 439.
(13) Dennis, N.; Katritzky, A. R.; Ramaiah, M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2281.
(14) Pirrung, F. O. H.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 5365.
(15) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211.
(16) (a) Pigeon, P.; Mamouni, A.; Sikoraiova, J.; Marchalin, S.; Decroix, B. *Tetrahedron* **2001**, *57*, 4939. (b) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424. (c) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (d) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775. (e) Boeck, B. D.; Jiang, S.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1994**, *50*, 7075. (f) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416.
(17) Yu, X.; Xu, J.; Zhoua, Y.; Song, Q. *Org. Chem. Front.* **2018**, *5*, 2463.

Downloaded by: University of Western Ontario. Copyrighted material.