

Consecutive multi-component syntheses of heterocycles via palladium-copper catalyzed generation of alkynones

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Dedicated to Prof. Dr. Alan R. Katritzky on the occasion of his 80th birthday

Abstract

Alkynones are prominent three-carbon building blocks in heterocyclic chemistry. They can be generated very easily and efficiently by modified *Sonogashira* coupling of acid chlorides and terminal alkynes. Mild reaction conditions now set the stage for new diversity-oriented routes to heterocycles by sequential and consecutive transformations. Hence, isoxazoles, indolizines, pyrazoles, pyrimidines, 1,5-benzoheteroazepines, furans, oxazoles, and tetrahydro- β -carbolines are accessible by consecutive coupling-cycloaddition or coupling-addition-cyclocondensation multi-component sequences.

Keywords: Alkynones, heterocycles, catalysis, cross-coupling, multi-component reactions

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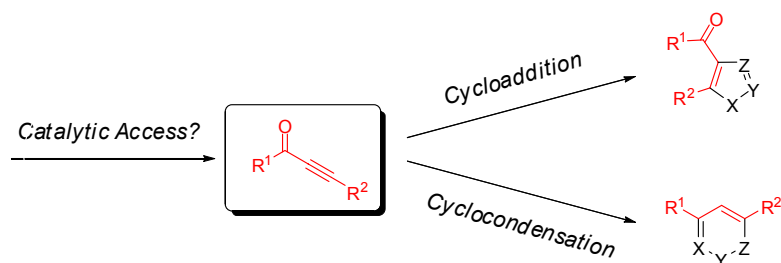
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References

1. Introduction

The increasing demand for rapid syntheses of functional and biologically active molecules has stimulated synthetic chemists to explore and devise intelligent strategies that inevitably address the very fundamental principles of efficiency and efficacy. Besides the crucial issues of chemo-, regio- and stereoselectivity, nowadays these processes also have to consider economical and ecological aspects of green chemistry. Therefore, the intellectual challenge to invent concise, elegant and conceptually novel synthetic routes has become a steadily increasing driving force both in academia and industry. In the past decade the productive concepts of multi-component processes have considerably stimulated the synthetic scientific community.¹⁻² In particular, these diversity-oriented syntheses³ are demanding challenges for synthetic efficiency and reaction design. Mastering unusual combinations of elementary organic reactions under similar conditions is the major conceptual challenge in crafting novel types of sequences.

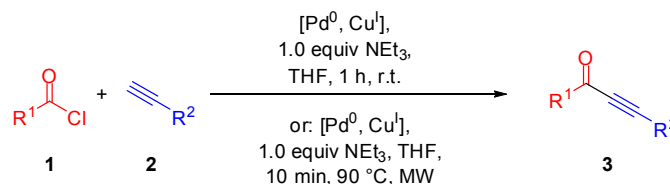
In classical heterocyclic chemistry, five-, six-, and seven-membered heterocycles can be synthesized from reactive, bifunctional three-carbon building blocks such as alkynones⁴⁻⁷ which react with bifunctional nucleophiles either via [3+2]-cycloaddition or via *Michael* addition-cyclocondensation (Scheme 1). As a consequence, this general strategy has found broad application. However, standard syntheses of alkynones⁸ are often harsh and require either strongly basic or strongly *Lewis* or *Brønsted* acidic conditions. Therefore, the application in one-pot methodology, where delicately balanced reaction conditions are prerequisite, is largely excluded. Hence, mild reaction conditions for a catalytic generation of alkynones, which are compatible with following transformations, are highly desirable. In particular, transition metal catalysis opens many opportunities for functional group tolerant product formations and multi-component syntheses of heterocycles.⁹ This account summarizes a concept developed in recent years in our group, where palladium-copper catalyzed coupling is used for the generation of alkynones and as an entry to consecutive multi-component syntheses of heterocycles.



Scheme 1. Alkynones as three-carbon building blocks in heterocycle synthesis and the quest for their catalytic generation.

2. Modified Sonogashira Coupling of Acid Chlorides to Alkynes

The *Sonogashira* coupling,¹⁰ a palladium-copper catalyzed alkynylation of (hetero)aryl halides, is a particularly mild alkyne synthesis and, hence, alkynones **3** can be easily prepared from acid chlorides **1** with terminal alkynes **2** (Scheme 2).¹¹



Scheme 2. Alkynones **3** by modified *Sonogashira* cross-coupling.

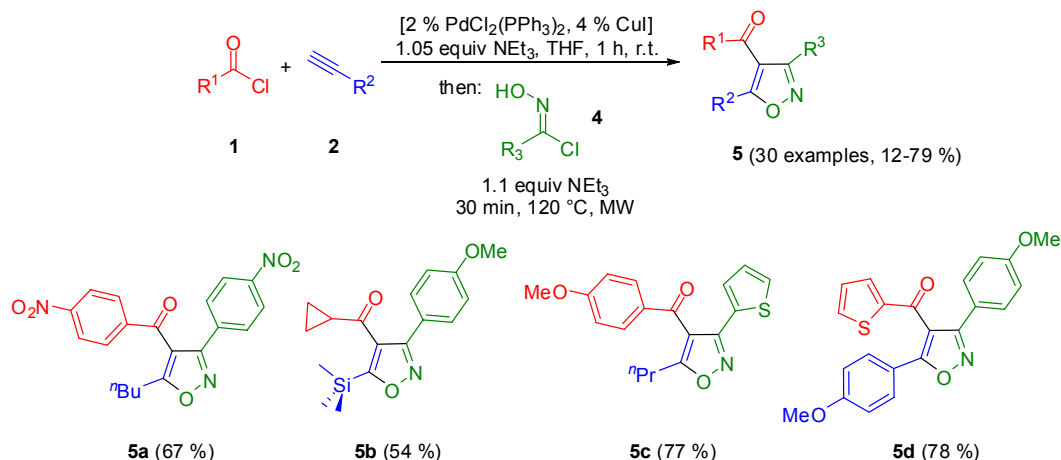
Upon scrutinizing the reaction conditions, we found that virtually only one equivalent of triethylamine is stoichiometrically necessary for binding hydrochloric acid, and hence, to achieve complete conversion.¹² This not only reduces the amount of base but also leads to an essentially base-free reaction medium after the cross-coupling event. Furthermore, it is also possible to reduce reaction time by dielectric heating (microwave irradiation) instead of conductive heating (oil bath). With this methodological improvement in hand the stage was set for the generation of alkynones under mild conditions and in media where consecutive reactions in a one-pot fashion are readily conceivable.

3. Multi-component Coupling-cycloaddition Sequences

3.1 Isoxazole syntheses

The 1,3-dipolar cycloaddition of aromatic nitrile oxides, a class of propargyl-type 1,3-dipoles, is a general access to isoxazoles.¹³ Since aromatic nitrile oxides are usually unstable compounds, it is necessary to generate them *in situ* by dehydrochlorination of the corresponding hydroximinoyl chlorides with a suitable base. If triethylamine is the base, this step should be fully compatible with a preceding alkyne formation.

Therefore, after reacting acid chlorides **1** with terminal alkynes **2** under modified *Sonogashira* conditions for 1 hour at room temperature to furnish the expected alkynones **3**, subsequently, hydroximinoyl chlorides **4** and triethylamine are added. After dielectric heating for 30 minutes, the isoxazoles **5** are obtained as in moderate to excellent yields often as crystalline solids. Only one of two possible regioisomers is formed (Scheme 3).¹⁴

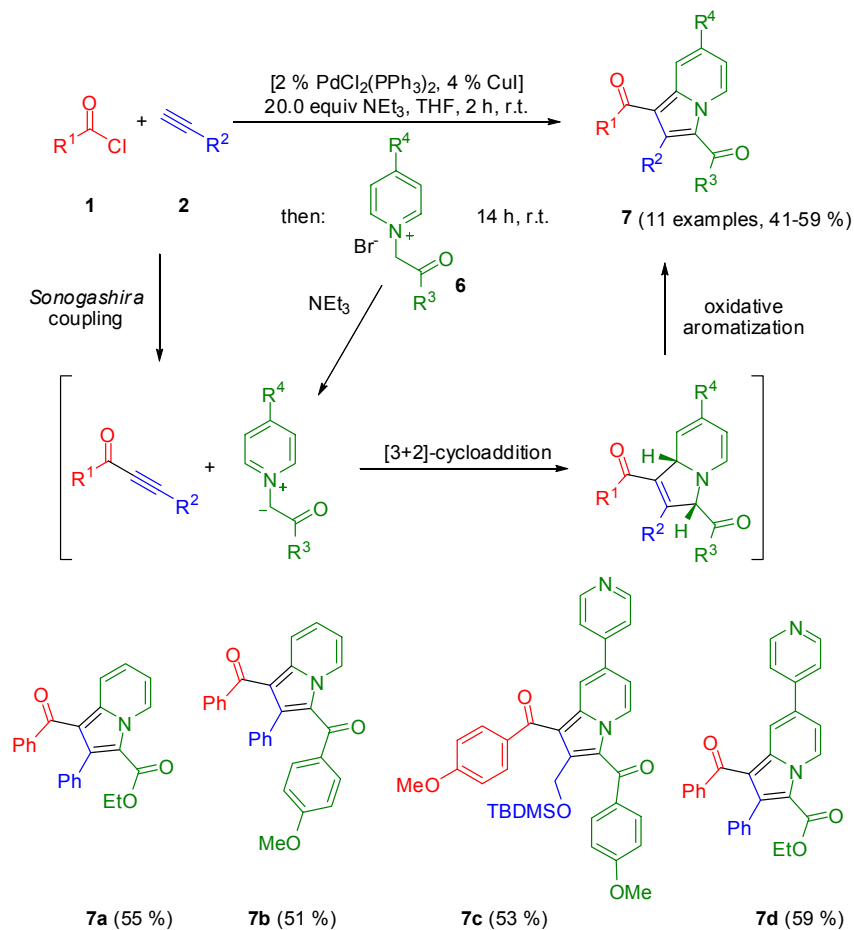


Scheme 3. Three-component synthesis of isoxazoles **5**.

The scope of this one-pot coupling–cycloaddition isoxazole synthesis is fairly broad and can be performed under mild conditions and with excellent chemo- and regioselectivity. As a consequence of acid chlorides as halide coupling partner, amines and hydroxy groups need to be protected prior to the reaction. The use of the acid chlorides **1** is predominantly limited to (hetero)aromatic compounds and derivatives without α -hydrogens. With one exception, cyclopropyl as substituent is tolerated in both steps of the sequence. Aliphatic as well as electron rich and electron poor aromatic alkynes can be employed. Even heterocyclic alkynes can be used as starting materials. Silylated alkynes, e. g. trimethylsilyl acetylene, also easily undergo the coupling procedure. With respect to the 1,3-dipolar nitrile oxide, electron-rich, polycyclic, electron-deficient and heterocyclic substituents are all tolerated and react readily with the alkynes **3**.

3.2 Indolizine syntheses

Pyridinium ylides, allyl-type 1,3-dipolar molecules, undergo [3+2]-cycloaddition with alkynes as well. Thus, submitting (hetero)aryl chlorides **1** and terminal alkynes **2** to the reaction conditions of the *Sonogashira* coupling in a mixture of THF and triethylamine at ambient temperature and after 2 h adding 1-(2-oxoethyl)pyridinium bromides **6** furnish after 14 h of stirring at room temperature indolizines **7** in 41-59 % yield as pale yellow to yellow green crystalline solids (Scheme 4).¹⁵



Scheme 4. Three-component synthesis of indolizines 7.

This reaction is a novel methodological showcase for the combination of a cross-coupling and a sequential cycloaddition, giving rise to a broad variety of indolizines 7. In particular, 7-(pyridin-4-yl)-substituted representatives display pronounced fluorescence and even strong day-light fluorescence in their protonated form. The reversibility of the protonation as well as its fluorescence sensitivity in weakly acidic media render 7-(pyridin-4-yl)indolizines ideal candidates for fluorescence labeling and for studying pH-dependent and pH-alternating cellular processes.

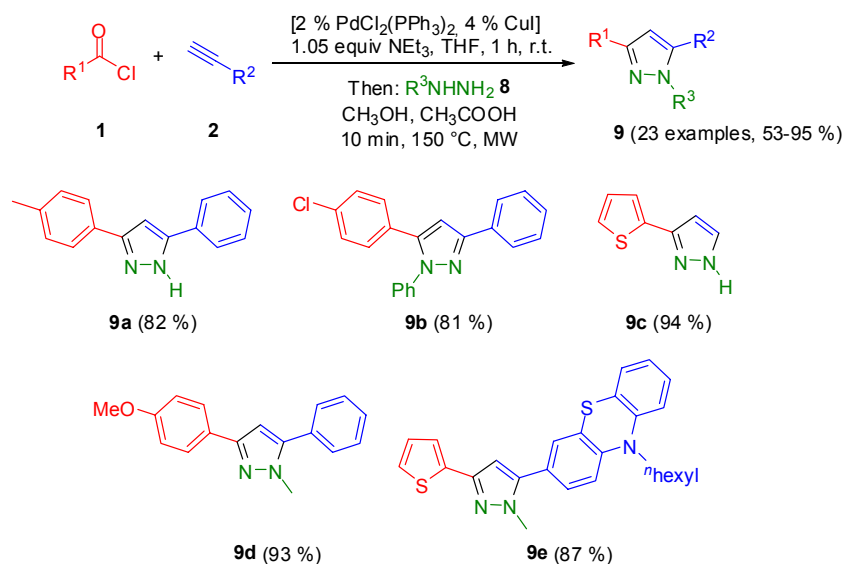
4. Multi-component Coupling-addition-cyclocondensation Sequences

4.1 Pyrazoles

The direct conversion of hydrazines 8 with alkynones 3 to pyrazoles by *Michael* addition-cyclocondensation has been known for more than a century.^{4a,16} However, either the regioselectivity issue has not been studied in detail or the occurrence of mixtures of regioisomers

was reported.¹⁷ Despite of very few examples,¹⁸ the regioselective formation of *N*-substituted pyrazoles by the alkynone pathway has remained unexplored. With respect to the interesting pharmacological and electronic properties of pyrazoles, in particular as fluorophores, and the increasing quest for tailor-made functional π -electron systems by diversity-oriented strategies, we have developed regioselective one-pot syntheses of substituted pyrazoles.

After formation of alkynones **3**, hydrazines **8**, and acetic acid are reacted in the same reaction vessel. Best results for the formation of pyrazoles **9** are obtained by dielectric heating in the microwave oven at 150 °C for 10 min in the presence of methanol. Pyrazoles **9** are obtained in good to excellent yields, predominantly as colorless crystalline solids (Scheme 5).¹⁹



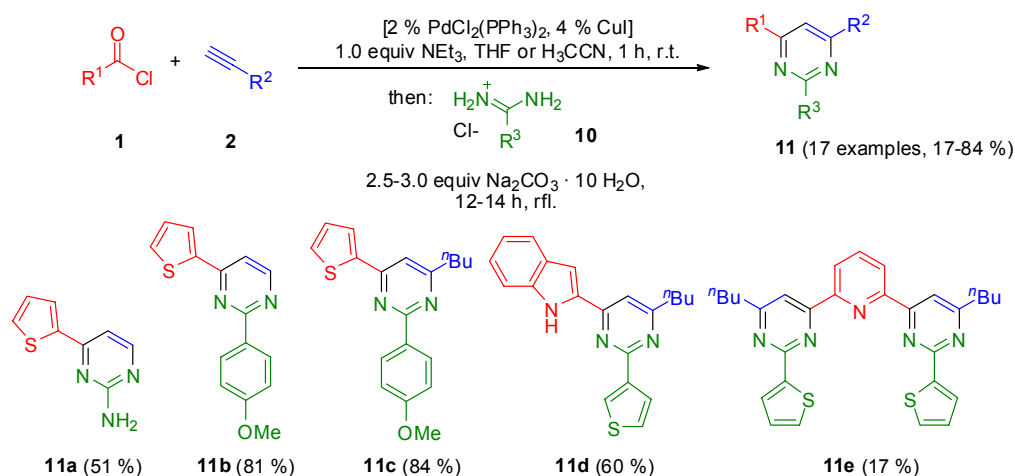
Scheme 5. Three-component synthesis of pyrazoles **9**.

Three types of hydrazines have been employed in the methodological studies, i.e. hydrazine ($R^3 = H$), methyl hydrazine ($R^3 = CH_3$), and aryl hydrazines ($R^3 = \text{aryl}$). In accordance with theory in every case only one of the two possible regioisomers, depending on the nature of the hydrazine substituent R^3 , was preferentially formed. Only traces of the other regioisomers could be detected (regioselectivity >98:2). The rapid, diversity-oriented synthetic approach to fine-tunable fluorophores (with fluorescence quantum yields up to 0.78) are of considerable interest for the development of tailor-made emitters in OLED applications and fluorescence labeling of biomolecules, surfaces or mesoporous materials.

4.2 Pyrimidines

As already indicated, alkynones **3** can be reacted without isolation with difunctional nucleophiles to furnish heterocycles. Amidines are bifunctional nucleophiles containing a three-atom building block and lead to the formation of six-membered heterocycles. Therefore, a consecutive three-component synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines **11** is based upon

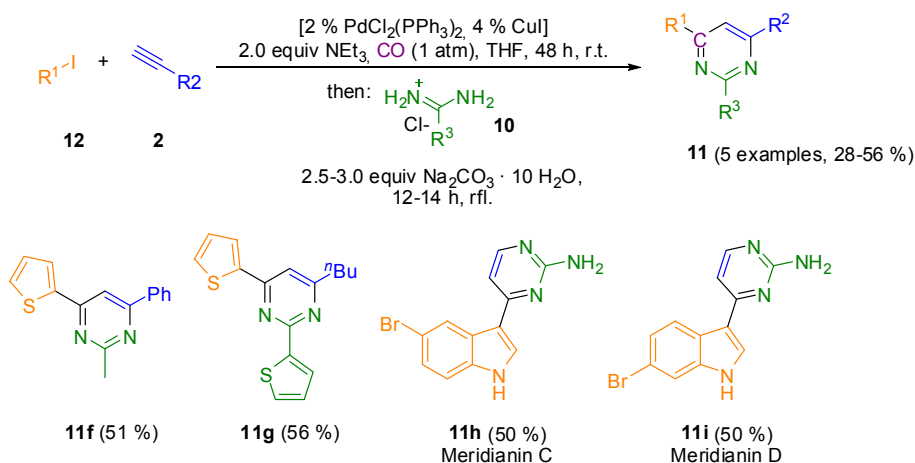
the sequence of *Sonogashira* coupling and subsequent cyclocondensation with amidinium salts **10** (Scheme 6).²⁰



Scheme 6. Three-component synthesis of pyrimidines **11**.

2-Amino pyrimidines like **11a** are readily formed by condensation with guanidine as binucleophile. Interestingly, this one-pot reaction can also be applied to furnish complex ligand type pyrimidines such **11e**.

An alternative catalytic three-component access to alkynones **3** can be conceived by carbonylative alkylation of aryl iodides **12**, terminal alkynes **2** and carbon monoxide.²¹ Upon subsequent addition of an amidinium salt **10** highly substituted pyrimidines **11** can be obtained in the sense of a four-component reaction (Scheme 7).²²

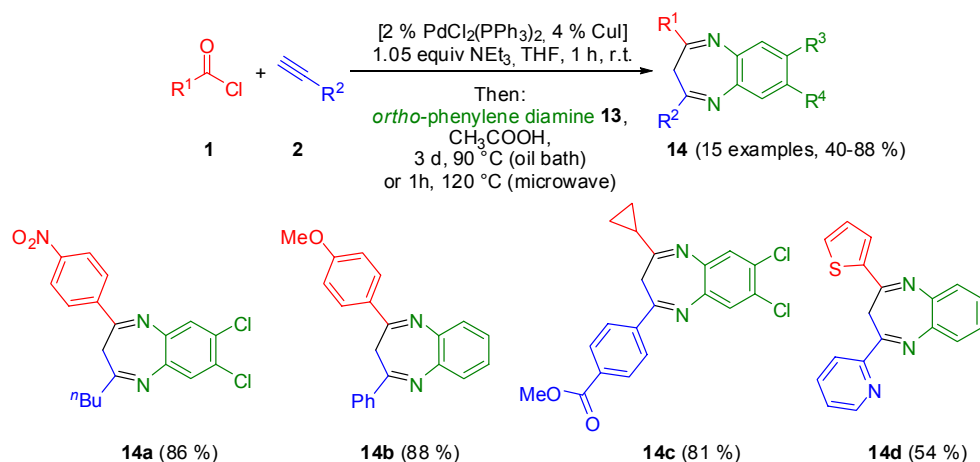


Scheme 7. Four-component synthesis of pyrimidines **11**.

Additionally, this approach, however, as a two step carbonylative alkynylation-cyclocondensation sequence, is applicable to concise syntheses of naturally occurring and highly biologically active meridianins **11h** and **11i**, and variolin analogues.²²

4.3 1,5-Benzodiazepines

The expansion to seven-membered heterocycles is accomplished by reaction of *ortho*-phenylene diamines **13** with in situ generated alkynones **3**. The corresponding products of this coupling-addition-cyclocondensation sequence are pharmacologically interesting 1,5-benzodiazepines **14** (Scheme 8).²³

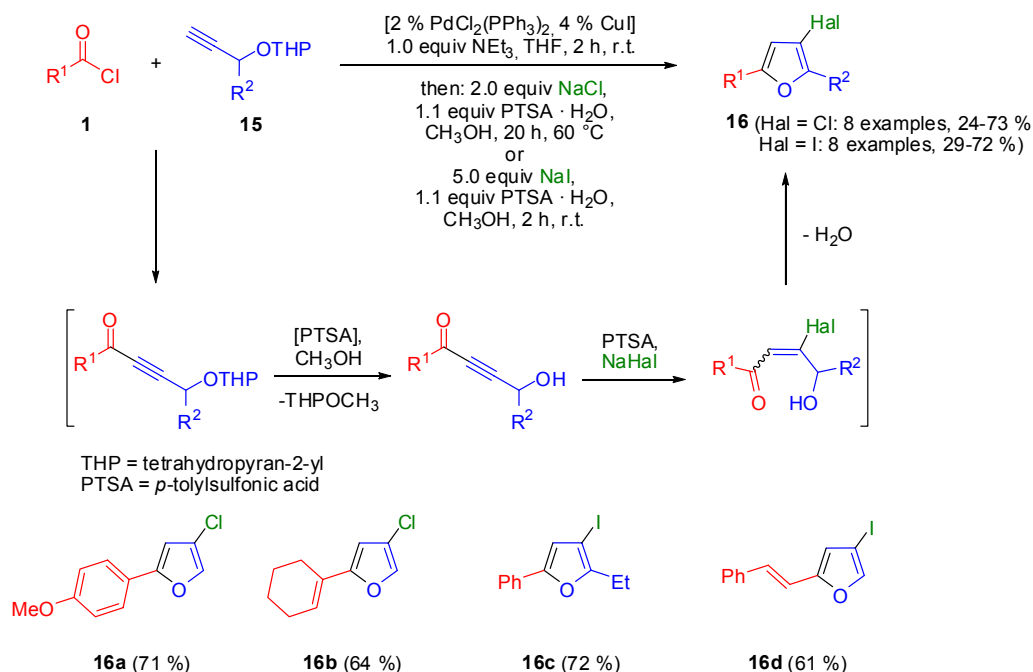


Scheme 8. Three-component synthesis of 1,5-benzodiazepines **14**.

In addition, all representatives are highly fluorescent in the solid state, however, essentially nonfluorescent in solution at room temperature. Upon cooling the solutions cryo-fluorescence is observed, which can be attributed to a freezing of the ring flip and aggregation. This thermoresponsive behavior of fluorophores as a consequence of restricted conformational changes opens new avenues for the development of tailor-made emitters in thermosensors and the fluorescence labeling of biomolecules, surfaces or mesoporous materials.

4.4 3-Halo furans and trisubstituted furans

A major consequence of the application of only one stoichiometrically necessary equivalent of triethylamine in the alkynone synthesis, is the essentially base free reaction medium. This peculiar circumstance has now paved the way to subsequent steps under *Lewis* or *Brønsted* acidic conditions, yet in a one-pot fashion. Therefore, in the sense of a sequence of *Sonogashira* coupling of acid chlorides **1** and THP-protected propargyl alcohols **15** and acid-mediated *Michael* addition to the alkynone intermediate **3** with concomitant deprotection and cyclocondensation 3-halo furans **16** are obtained in moderate to good yields (Scheme 9).²⁴

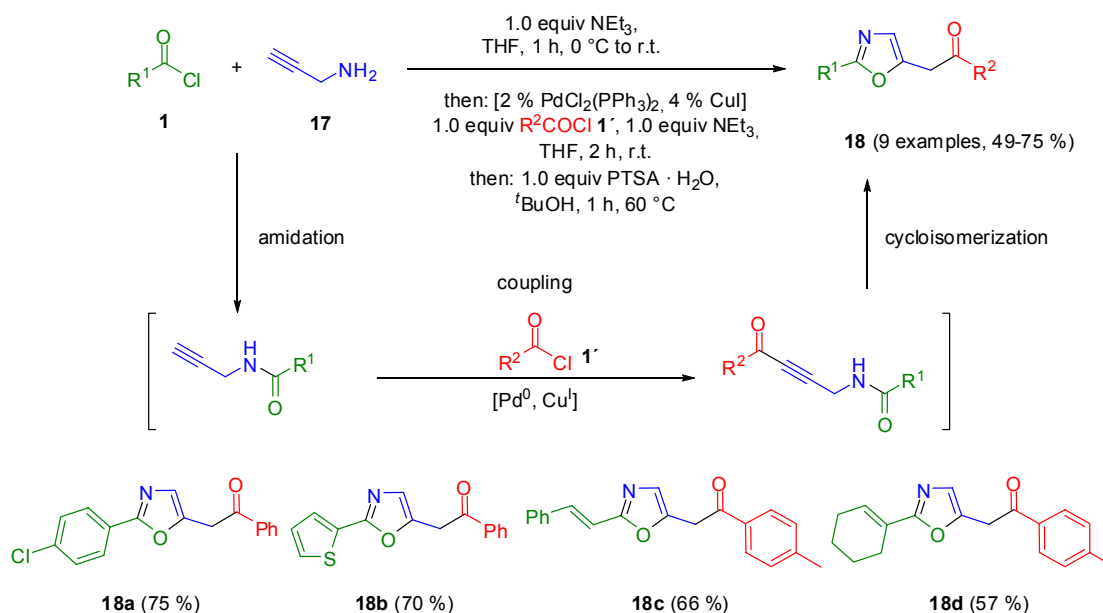


Scheme 9. Three-component synthesis of 3-halo furans **16**.

This reaction is an example for a hydrohalogenation to a *Michael* system. Likewise, iodine monochloride as an electrophilic iodine source on its own right, opens a straightforward access to 3-chloro-4-iodo furans.^{24b} It is noteworthy to mention that the 3-iodo furans **16** (Hal = I) can be coupled with boronic acids in a *Sonogashira*-addition-cyclocondensation-*Suzuki* sequence in a one-pot fashion, since the palladium catalyst system is still active after the acid-mediated cyclocondensation steps.^{24a}

4.5 Oxazoles

Propargyl amine **17** is readily amidated with acid chlorides **1** under mild reaction conditions to furnish amide protected propargyl amines. Without isolation these propargylamides are reacted with acid chlorides **1'**, and via alkyne intermediates **3** a proton catalyzed cycloisomerization gives rise to the formation of functionalized oxazoles **18** in good yields in the sense of an amidation-coupling-cycloisomerization sequence (Scheme 10).²⁵



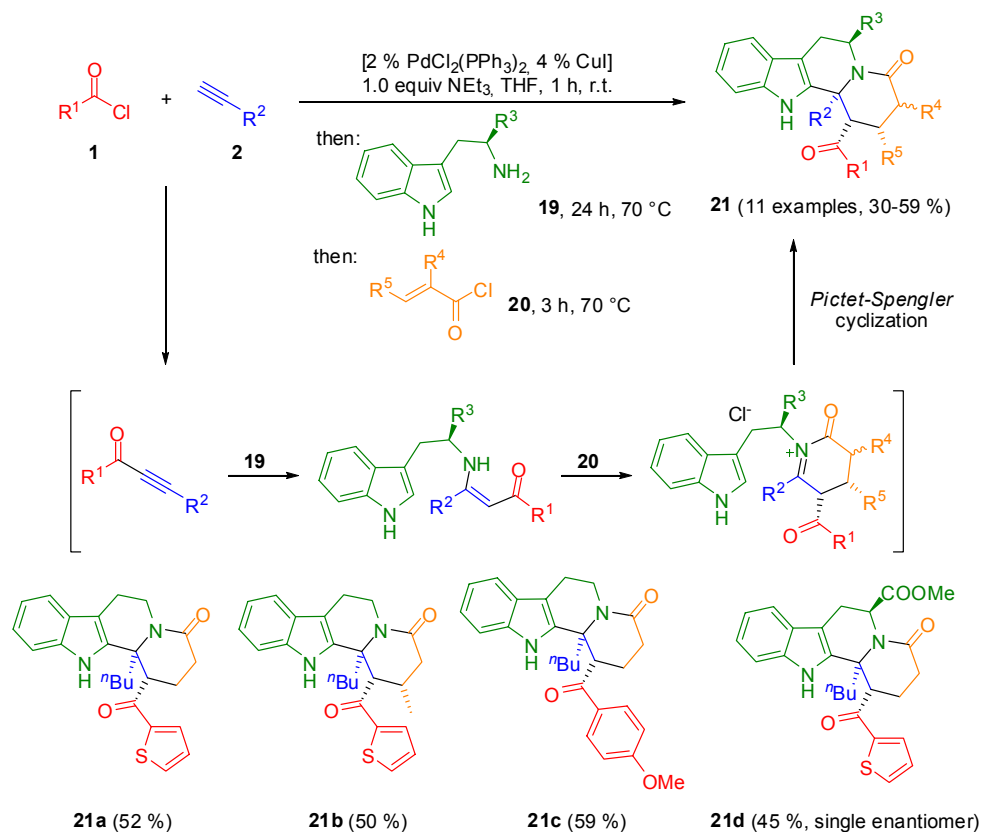
Scheme 10. Three-component synthesis of oxazoles **18**.

As already discussed for the pyrimidine syntheses, this process can also be conducted in the sense of a four-component amidation–carbonylative alkynylation–cyclization (ACACI) sequence. Studies addressing 1-substituted propargyl amines as substrates for the synthesis of more complex oxazoles are currently under investigation.

4.6 Tetrahydro- β -carbolines

In agreement with the fundamental principles of multi-component reactions, products of consecutive transformations are expected to contain substantial fragments of all starting materials, thus providing a high degree of atom-efficiency. Hence, β -enaminones in heterocyclic synthesis should be considered to be more than just synthetic equivalents of 1,3-dicarbonyl compounds. This aspect can be easily envisioned if one takes advantage of the unique electronically amphoteric reactivity of β -enaminones trying to conserve all atoms in the final product, including the enamino nitrogen atom.

In particular, the consecutive four-component reaction of acid chlorides **1**, alkynes **2**, tryptamine derivatives **19** and α,β -unsaturated acid chlorides **20** in the one-pot synthesis of tetrahydro- β -carbolines **21** most clearly demonstrates the potential of this concept and methodology for the rapid construction of highly-substituted, complex heterocycles where 5 new σ -bonds and 4 new stereocentres can be installed in a sequence of consecutive one-pot transformations (Scheme 11).²⁶ The final key step of this sequence is an aza-annulation reaction that presumably generates an acyliminium ion which concludes the sequence by a *Pictet–Spengler* cyclization.



Scheme 11. Four-component synthesis of tetrahydro- β -carbolines **21**.

5. Conclusion and Outlook

Transition metal catalysis has considerably fertilized the development of diversity-oriented synthesis of heterocycles, namely by disclosing new transition metal catalyzed multi-component reactions. Besides purely insertion based domino processes, sequential and consecutive one-pot reactions have significantly expanded the playground for reaction design. Conceptually, many applications such as in natural product synthesis, in medicinal chemistry, for the design of functional fluorescent and redox active molecular materials, or in ligand syntheses for catalysis and coordination chemistry can be tackled by transition metal catalyzed multi-component reactions of heterocycles. Still many other transition metal complexes, that are known to catalyze uni- and bimolecular transformations, are waiting to be discovered for inventing new sequences. Undoubtedly, the future holds surprising processes in store.

Acknowledgements

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References

1. For a recent monograph, see *e.g.* *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
2. For reviews, see *e. g.* (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (e) Ugi, I.; Dömling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (f) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (g) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (h) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour*, **1994**, *18*, 115. (i) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.
3. For reviews on diversity oriented syntheses, see *e.g.* (a) Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609. (b) Müller, T. J. J. In *Functional Organic Materials. Syntheses, Strategies, and Applications*, Müller, T. J. J.; Bunz, U. H. F., Eds, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2007, p179. (c) Schreiber, S. L.; Burke, M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 46. (d) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (e) Arya, P.; Chou, D. T. H.; Baek, M. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 339. (f) Cox, B.; Denyer, J. C.; Binnie, A.; Donnelly, M. C.; Evans, B.; Green, D. V. S.; Lewis, J. A.; Mander, T. H.; Merritt, A. T.; Valler, M. J.; Watson, S. P. *Progr. Med. Chem.* **2000**, *37*, 83. (g) Schreiber, S. L. *Science* **2000**, *287*, 1964.
4. For syntheses of pyrazoles, see *e.g.* (a) Moureu, C.; Delange, R. *Bull. Soc. Chim. Fr.* **1901**, *25*, 302. (b) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.* **1993**, *30*, 755. (c) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem.* **2002**, *67*, 9200.
5. For syntheses of isoxazoles, see *e.g.* (a) Bowden, K.; Jones, E. R. H. *J. Chem. Soc.* **1946**, *25*, 953. (b) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303.
6. For syntheses of pyrimidines, see *e.g.* (a) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *Chem. Commun.* **1997**, 1757. (b) Bagley, M. C.; Hughes, D. D.; Taylor, P.

- H.; Xiong, X. *Synlett* **2003**, 259. (c) Bagley, M. C.; Hughes, D. D.; Sabo, H. M.; Taylor, P. H.; Xiong, X. *Synlett* **2003**, 1443.
- For syntheses of pyridines, see e.g. (a) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265. (b) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Philips, N. G.; Xiong, X.; Bower, J. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663. (c) Bagley, M. C.; Dale, J. W.; Ohnesorge, M.; Philips, N. G.; Xiong, X.; Bower, J. J. *Comb. Chem.* **2003**, *5*, 41.
 - For a review, see: Nelson, A. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2005, Vol. 26, p. 971.
 - For reviews on transition metal catalyzed multi-component syntheses of heterocycles, see (a) D'Souza, D. M.; Müller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095. (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.
 - For lead reviews on Sonogashira couplings, see e.g. (a) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N.; *Synthesis* **1980**, 627. (b) Sonogashira, K. in *Metal Catalyzed Cross-coupling Reactions*, Diederich, F.; Stang, P. J. Eds.; Wiley-VCH, Weinheim, 1998, p 203 (c) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653 (1-2)*, 46. (d) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (e) Marsden, J. A.; Haley M. M. in *Metal Catalyzed Cross-coupling Reactions*, de Meijere, A.; Diederich, F. Eds.; Wiley-VCH, Weinheim, 2004, p 319 (f) Doucet, H.; Hierso, J.-C.; *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (g) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
 - Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.
 - D'Souza, D. M.; Müller, T. J. *J. Nat. Protoc.* **2008**, accepted for publication. (b) Karpov, A. S.; Müller, T. J. *J. Org. Lett.* **2003**, *5*, 3451.
 - (a) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839. (b) Jaeger, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Chemistry of Heterocyclic Compounds; Wiley: Hoboken, 2002; Vol. 59, p 361.
 - Willy, B.; Rominger, F.; Müller, T. J. *J. Synthesis* **2008**, 293.
 - Rotaru, A. V.; Druta, I. D.; Oeser, T.; Müller, T. J. *Helv. Chim. Acta* **2005**, *88*, 1798.
 - Claisen, L. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3664.
 - Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L. *J. Org. Chem.* **2002**, *67*, 9200.
 - Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43.
 - Willy, B.; Müller, T. J. *J. Eur. J. Org. Chem.* **2008**, 4157.
 - (a) Karpov, A. S.; Müller, T. J. *J. Org. Lett.* **2003**, *5*, 3451. (b) Karpov, A. S.; Müller, T. J. *J. Synthesis* **2003**, 2815.
 - Ahmed, M. S. M.; Mori, A. *Org. Lett.* **2003**, *5*, 3057. (b) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487.
 - Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6951.

23. (a) Willy, B.; Dallos, T.; Rominger, F.; Schönhaber, J.; Müller, T. J. J. *Eur. J. Org. Chem.* **2008**, 4796. (b) Palimkar, S. S.; Lahoti, R. J.; Srinivasan, K.V. *Green Chem.* **2007**, 9, 146.
24. Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2005**, 2581. (b) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Eur. J. Org. Chem.* **2006**, 2991.
25. Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817.
26. (a) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *Org. Biomol. Chem.* **2005**, 4382. (b) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502.

Authors' biographies



Benjamin Willy was born in Karlsruhe, Germany, in 1980 and studied chemistry at the Ruprecht-Karls-Universität Heidelberg from 2000 to 2005. He obtained his Diploma in 2005 under the supervision of Prof. T. J. J. Müller. He continued with his graduate studies in the same group at the University of Heidelberg and since October 2006 at the Heinrich-Heine-Universität Düsseldorf. Currently, he is finishing his Ph. D. thesis on synthetic and methodological investigations towards new multi-component syntheses of fluorescent heterocycles. His research interests encompass synthetic organic chemistry, transition metal catalysis and tailor-made fluorophores.



Thomas J. J. Müller was born in Würzburg, Germany, in 1964 and studied chemistry at the Ludwig-Maximilians-Universität München (LMU) from 1984 to 1989. He obtained his Diploma in 1989 and completed his Ph.D. in 1992 with Prof. R. Gompper on novel cyanine systems as models for optical switches and molecular metals. After a post-doctoral stay with Prof. B. M. Trost at Stanford University (USA) in 1993 and 1994 working on ruthenium-catalyzed Alder-ene reactions, he returned to Germany. In 1994, as a Liebig scholar he began his independent research at the Technical University Darmstadt, moved to LMU as a DFG scholar in 1997, to obtain his habilitation and was appointed to Privatdozent in 2000. In 1999/2000 he was acting professor at the University of Stuttgart. From 2002 to 2006 he was a professor of organic chemistry at the Ruprecht-Karls-Universität Heidelberg. Since 2006 he holds the chair of organic chemistry at the Heinrich-Heine-Universität Düsseldorf. His research interests encompass synthetic heterocyclic chemistry, its implication for developing novel tailor-made chromophores, nanometer-sized redox active molecules, and the design of novel multi-component and domino reactions.