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Copper-Catalyzed Transformation of Hydrazones into Halogenated Azabutadienes, Versatile Building Blocks for Organic Synthesis

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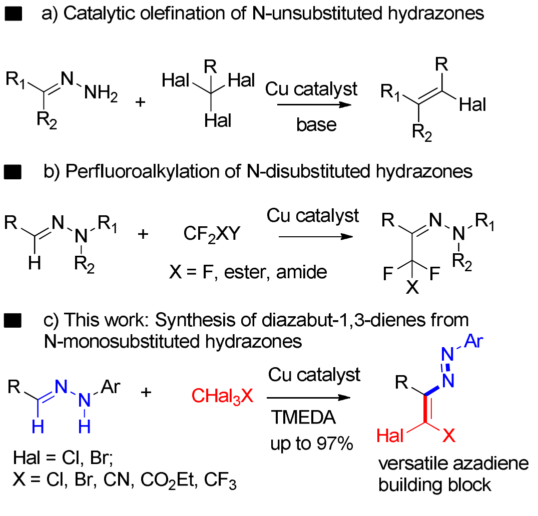
ABSTRACT: A one-step copper-catalyzed reaction of aldehyde-derived *N*-substituted hydrazones with CCl_4 resulted in efficient synthesis of 4,4-dichloro-1,2-diazabuta-1,3-dienes. It was proven that this C-C bond forming cascade reaction operates via an addition of trichloromethyl radical to the C=N bond of hydrazone followed by a base-induced elimination of HCl. The reaction was found to be very general, as diverse hydrazones possessing various aromatic groups at *N*-site, as well as aromatic, aliphatic and heterocyclic substituents at *C*-site, are capable partners for coupling with a wide range of polyhalogenated compounds (CCl_3Br, CBr_4, CCl_3CN, CCl_3COOEt, CCl_3CF_3, CBr_3CF_3) to produce a family of functionalized 1,2-diazabuta-1,3-dienes. It was demonstrated that the prepared heterodienes are highly versatile building blocks for straightforward assembly of various valuable acyclic and heterocyclic molecules.

KEYWORDS: homogeneous catalysis, hydrazones, copper, heterodiene, reaction mechanisms

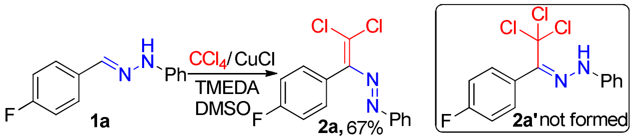
Hydrazones are important class of carbonyl derivatives exhibiting diverse chemical behavior. These "chemical chameleons" are reactive towards nucleophiles, electrophiles, radicals, and carbenes. Nowadays, hydrazone functionality is widely used in modern organic chemistry,[1] material science,[2] as well as in medicinal chemistry.[3] Some time ago, we discovered a novel catalytic olefination reaction, the copper-catalyzed coupling of *N*-unsubstituted hydrazones with polyhalogenated alkanes (Scheme 1, a).[4] This transformation became an efficient method for construction of various functionalized alkenes. More recently, application of this strategy to other copper-[5] and palladium-catalyzed[6] transformations, including trifluoromethylations and difluoroalkylations of *N*-disubstituted hydrazones, appeared in the literature (Scheme 1, b). Herein, we report an unexpected reaction of monosubstituted hydrazones with carbon tetrachloride and other polyhalogenated compounds to produce 1,2-diaza-1,3-dienes, which are a highly versatile heterodiene synthons (Scheme 1, c).

Aiming at the expanding the scope of the carbon-carbon bond forming protocols involving hydrazones, we studied reactions of monosubstituted hydrazones with carbon tetrachloride and other polyhalogenated compounds.



Scheme 1. Reported and novel reactivity of hydrazones with polyhalogenated compounds.

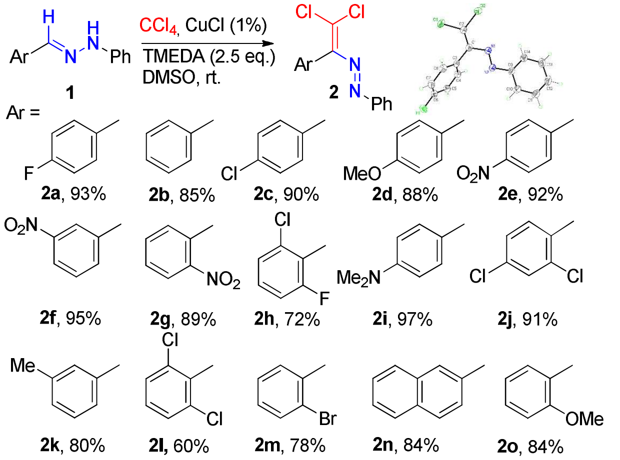
However, the reaction of hydrazone **1a** with CCl_4 in the presence of catalytic amounts of CuCl[7] followed an unanticipated path. Thus, instead of expected trichloromethylated hydrazone **2a'**, the azadiene product **2a** was isolated in 67% yield! The structure of **2a** possessing trans-configuration of the aza-fragment was unambiguously confirmed by the single crystal X-ray analysis (Scheme 2).



Scheme 2. Initial discovery.

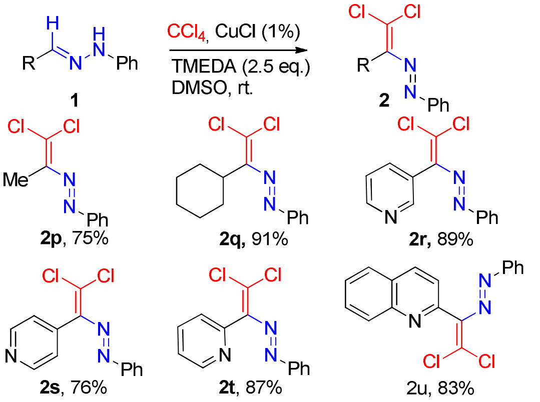
Notably, 1,2-diaza-1,3-dienes are extremely attractive synthons for construction of various types of heterocycles.[8] Motivated by the importance of heterodienes,[8] and inspired by our successful preliminary result, we further explored this interesting transformation.

After exhaustive optimization studies,[9] it was found that most efficiently the reaction proceeds with excess CCl_4 (10 eq.) in DMSO at room temperature in the presence of 1-2 mol % of CuCl and 2.5 equivalents of TMEDA. With the optimized reaction conditions in hand, the scope of this new reaction was investigated (Scheme 3). First, the influence of the nature of the carbonyl part of phenyl hydrazones was examined. Thus, a number of hydrazones derived from benzaldehydes 1 possessing both sterically and electronically different substituents were tested. Gratifyingly, the reaction appeared to be very general working perfectly well with hydrazones prepared from either electron rich- or electron poor benzaldehydes to produce the desired products in high isolated yields (up to 97%). Apparently, the electronic factors at benzaldehyde part did not affect the reaction since all hydrazones were smoothly converted to the final products. The reaction with naphthalene derivative also proceeded well to produce **2n** in 84% yield. Probably due to steric reason, the reaction of hydrazone of 2,6-dichlorobenzaldehyde **2l** showed somewhat lower efficiency (60%).



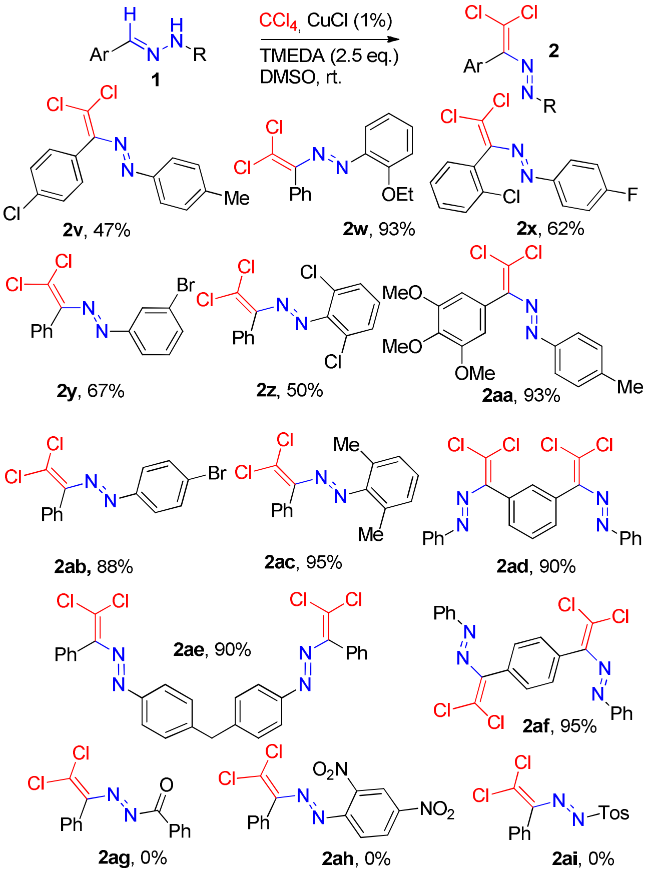
Scheme 3. Scope of arylaldehyde hydrazones and molecular structure of 2a.

Next, a possibility for employment of substrates beyond benzaldehyde derived hydrazones was investigated (Scheme 4). To this end, hydrazones of aliphatic aldehydes, as well as some heterocyclic derivatives (pyridine, quinoline and furan), were tested. The reactions of hydrazones of acetaldehyde and cyclohexyl carbaldehyde were very efficient, giving 75 and 91% yields, respectively. Likewise, substrates possessing differently substituted pyridines and quinoline reacted smoothly to produce the corresponding heterocyclic azadiene products in good to excellent yields.



Scheme 4. Scope of aliphatic and heteroaromatic aldehyde derived hydrazones.

Next, the nature of the hydrazine fragment was examined. It was found that in contrast to the aldehyde moiety, which virtually had no effect on the reaction, the hydrazine part had a substantial influence on the reaction outcome. (Scheme 5)



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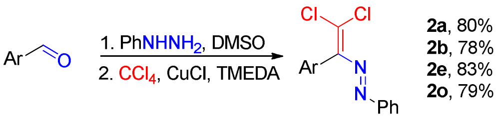
Scheme 5. Scope of hydrazine fragment.

Thus, the transformation with substrates possessing electron poor aryl groups proceeded much more sluggishly (**2z**) or did not proceed at all (**2ag-ai**). Nonetheless, a part of the cases mentioned above, the variation of hydrazine part is quite broad allowing for the preparation of a diverse set of heterodienes.

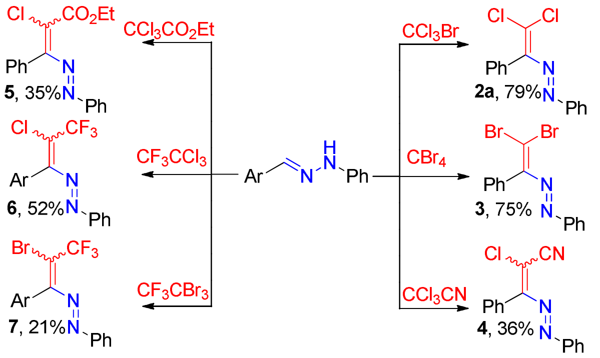
The reaction is also applicable for synthesis of bis-heterodienes (**2ad-af**).

Also, the possibility to perform the reaction under much more synthetically attractive one-pot protocol starting from easily available benzaldehydes and hydrazines was investigated (Scheme 6). Gratifyingly, the reactions proceeded very efficiently producing heterodienes **2a,b,e,o** in good yields, which were comparable with those obtained under the standard protocol that employs the pre-synthesized hydrazones (Scheme 3).



Scheme 6. One-pot transformation of benzaldehydes into heterodienes 2.

Then, the scope of this transformation was further tested in the reaction of *N*-monosubstituted hydrazones with other polyhalogenated compounds including those possessing ester-, cyano-, and trifluoromethyl groups (Scheme 7). We were pleased to find that under unoptimized conditions, a set of interesting azadienes **3-7** was obtained. These results indicate that this reaction has a wide scope, giving access to a broad range of attractive heterodienes, including trifluoromethylated derivatives **6** and **7**, potentially useful building blocks for medicinal chemistry, agrochemistry, and materials science.[10]

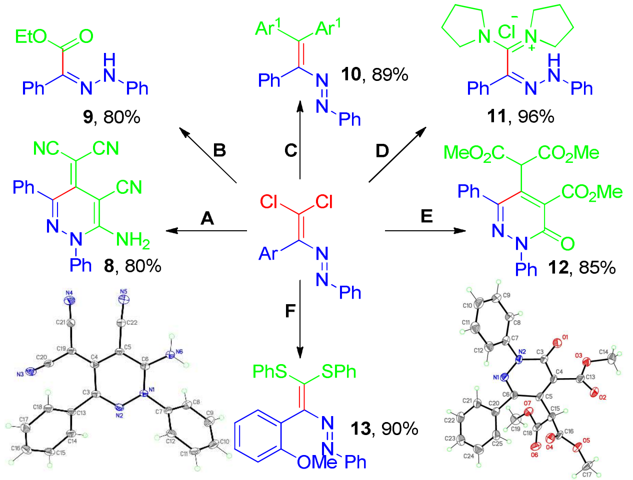


Reactions conditions: DMSO, rt, 10h, 10 eq. of polyhalogenated alkane, 2.5 eq. TMEDA. Ar= 4-FC$_6$H$_4$-

Scheme 7. Scope of polyhaloalkanes.

Apparently, due to the presence of the electron-withdrawing aza-group, the obtained aza-dienes **2** are profound electrophiles. Accordingly, our initial studies of the synthetic usefulness of these potentially attractive synthons were investigated in reactions with *O*-, *N*-, *S*-, and *C*-nucleophiles (Scheme 8). These reactions followed different scenarios, including substitution of Cl atoms with nucleophiles (paths C and F), the formation of hydrazo-derivatives (B and D), and heterocyclizations with participation of an azo-group (A and E). The last pathway looks especially attractive for the preparation of some heterocyclic systems, such as pyridazines.

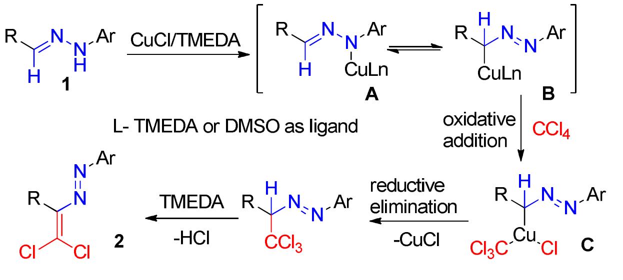
It was found that all these reactions proceeded very efficiently to give the corresponding products **8-13** in 80 to 96% yields. Notably, only limited examples of such dienes bearing a leaving group, which provides an additional handle for further functionalization, have been described previously.[11] On the other hand, highly valuable products, which is difficult to prepare using alternative methods, can be obtained in one synthetic step from aza-dienes **2** in high yields.



Reaction conditions **A**: CH$_2$(CN)$_2$, NaH, THF, rt, 5h. **B**: EtOH, reflux, 2h. **C**: Ar^1=4-EtOC$_6$H$_4$-. Suzuki reaction, Ar^{1}B(OH)$_2$, S-Phos, K$_3$PO$_4$, toluene, rt, 6h **D**: pyrrolidine, THF, rt, 5h. **E**: dimethyl malonate, NaH, THF, rt, 5h. **F**: PhSH, NaH, THF, rt, 6h.

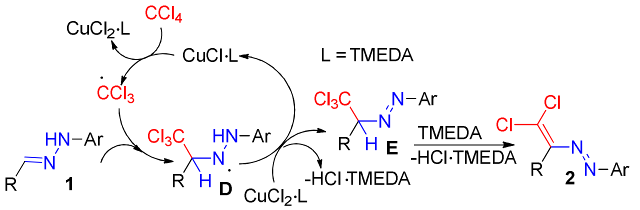
Scheme 8. Synthetic transformations of azadienes 2 and molecular structures of 8 and 12.

Finally, initial efforts have been made to bring insight into possible mechanism of this reaction. We foresee two most plausible distinct scenarios for this transformation. First would involve the Cu(I)/Cu(III) manifold (Scheme 9), according to which the reaction of **1** and Cu(I) salt produces the *N*-copper hydrazide **A**, existing in equilibrium with organocopper intermediate **B**. The latter, upon oxidative addition with CCl$_4$, forms Cu(III) intermediate **C**, which after reductive elimination followed by an elimination of HCl, delivers the reaction product **2**. However, the performed ESR studies under strict anaerobic conditions[9] indicated the presence of Cu^{2+} species, thus contradicting with this mechanistic path. Also we tried to detect the formation of *N*-copper hydrazide **A** in the reaction of CuCl with hydrazones **1** in the presence of TMEDA. However, accordingly to NMR data, such species were not detected even in the case of hydrazones having additional coordination site (2-pyridine carbaldehyde derived hydrazone).



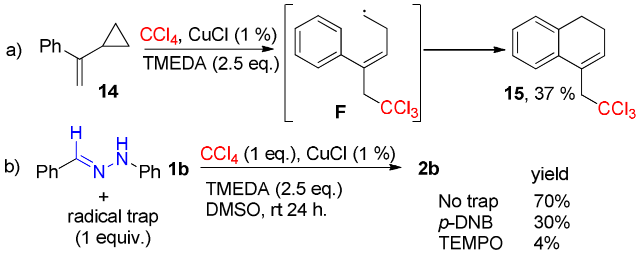
Scheme 9. Mechanism including participation of Cu (I)/Cu(III) species.

An alternative SET-involved scenario operates via Cu(I)/Cu(II) catalytic cycle (Scheme 10).[12] First, the SET from CuCl to CCl$_4$ generates Cu(II) species and the CCl$_3$ radical.[13] The latter, adds to the C=N bond of hydrazone **1** to produce the *N*-centered hydrazonyl radical **D**,[14] with upon oxidation by Cu(II) and loss of HCl, is converted into the diazene **E**. A subsequent TMEDA-assisted elimination of another molecule of HCl from **E** furnishes the reaction product, 1,2-diaza-1,3-diene **2**.



Scheme 10. SET mechanism including participation of Cu (I)/Cu(II) species.

As mentioned above, the performed ESR studies confirmed the presence of Cu(II) species in the reaction mixture.[9] In order to validate the presence of radical intermediates in this transformation, the radical clock experiments were performed (Scheme 11, a). It was found that the reaction of α-cyclopropyl styrene **14** with CCl_4 under our standard conditions produced dehydronaphthalene **15** in moderate yield. It is apparent that the latter originates from oxidative cyclization[15] of the radical **F** at the phenyl ring, which is formed upon addition of the CCl_3 radical to **14**. This result provides strong support for the participation of the CCl_3 radical in this transformation. The radical nature of this reaction was further supported by the experiments in the presence of radical scavengers. Thus, it was found that addition of 1 equivalent of *p*-DNB substantially inhibits the reaction, whereas the addition of TEMPO virtually shuts down this reaction (Scheme 11, b).



Scheme 11. Preliminary mechanistic studies supporting SET mechanism.

In summary, the new carbon-carbon bond forming reaction of *N*-monosubstituted hydrazones with polyhaloalkanes to produce 1,2-diazabuta-1,3-dienes has been developed. This highly efficient copper-catalyzed transformation features a broad scope with regard to all reaction components, as well as the possibility to perform the process in a much more convenient one-pot fashion starting with easily available aldehydes and hydrazines. The synthetic usefulness of the obtained halogenated azadienes was demonstrated in their reactions with *O*-, *N*-, *S*- and *C*-nucleophiles, which opened access to a variety of valuable acyclic and heterocyclic products. Mechanistic studies revealed that this Cu-catalyzed transformation proceeds via radical pathway. Further investigations of the synthetic applications of the obtained halogenated azadienes, as well as mechanistic studies toward better understanding the mechanism of this novel transformation are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, X-Ray and UV-data, ^{1}H-NMR and ^{13}C-NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

VMG, SVS, VMM, AIL and AVS performed the experiments; PVD and VNK are responsible for the X-ray analysis; VMG and VMM wrote the SI; AVS and VGN conceived the idea and VGN wrote the manuscript. All authors have given approval to the final version of the manuscript.

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REFERENCES

[1] (a) Hidai, M.; Mizobe, Y. *Chem. Rev.* **1995**, *95*, 1115-1133. (b) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157-169. (c) Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386-1434. (d) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626-2704.

[2] (a) Lehn, J.-M. *Chem. Soc. Rev.* **2007**, *36*, 151-160. (b) Lehn, J.-M. In *Topics in Current Chemistry*, Barboiu, M. Ed.; Springer, Berlin, 2012; vol. 322, p. 1-32. (c) Lehn, J.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2836-2850. (d) Su, X.; Aprahamian, I. *Chem. Soc. Rev.* **2014**, *43*, 1963-1981.

[3] (a) Verma, G.; Marella, A.; Shaquiquzzaman, M.; Akhtar, M.; Ali, M. R.; Alam, M. M. *J. Pharm. Bioallied Sci.* **2014**, *6*, 69-80. (b) Negi, V. J.; Sharma, A. K.; Negi, J. S.; Ram, V. *Int. J. Pharm. Chem.* **2012**, *4*, 100-109. (c) Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. *Eur. J. Med. Chem.* **2002**, *37*, 553-564. (d) Loncle, C.; Brunel, J.; Vidal, N.; Dherbomez, M.; Letourneux, Y. *Eur. J. Med. Chem.* **2004**, *39*, 1067-1071. (e) Savini, L.; Chiasserini, L.; Travagli, V.; Pellerano, C.; Novellino, E.; Cosentino, S.; Pisano, M. *Eur. J. Med. Chem.* **2004**, *39*, 113-122. (f) Cocco, M.; Congiu, C.; Lilliu, V.; Onnis, V. *Bioorg. Med. Chem.* **2006**, *14*, 366-372. (g) Masunari, A.; Tavares, L. C. *Bioorg. Med. Chem.* **2007**, *15*, 4229-4236. (h) Vicini, P.; Incerti, M.; La Colla, P.; Loddo R. *Eur. J. Med. Chem.* **2009**, *44*, 1801-1807.

[4] See reviews (a) Nenajdenko, V. G.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *Russ. Chem. Bull.* **2004**, *53*, 1034-1064. (b) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V. *Chem. Rev.* **2015**, *115*, 973-1050.

[5] (a) Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *ACS Catal.* **2016**, *6*, 1093-1096. (b) Pair, E.; Monteiro, N.; Bouyssi, D.; Baudoin, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 5346-5349. (c) Ke, M.; Song, Q. *J. Org. Chem.* **2016**, *81*, 3654-3664. (d) Prieto, A.; Landart, M.; Baudoin, O.; Monteiro, N.; Bouyssi, D. *Adv. Synth. Catal.* **2015**, *357*, 2939-2943.

[6] Prieto, A.; Melot, R.; Bouyssi, D.; Monteiro, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 1885-1889.

[7] Some recent reviews by Cu-catalyzed transformations: (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234-6458. (b) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525-3550. (c) Kozlowski, M. C. In *Copper-Oxygen Chemistry*, Karlin, K. D., Itoh, S., Eds.; Wiley: Hoboken, NJ, 2011; pp-361-444. (d) Cho, S. H.; Kim, J. Y.; Kwak, J. *Chem. Soc. Rev.* **2011**, *40*, 5068-5083. (e) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302-1315. (f)

Patil, N. T.; Yamamoto, Y. *Chem. Rev*. **2008**, *108*, 3395-3442. (g) Chemler, S. R. *Science* **2013**, *341*, 624-626.

[8] See reviews and book chapters: (a) Attanasi, O. A.; Crescentini, L. D.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem*. **2009**, 3109-3127. (b) Attanasi, O. A.; Caglioti, L. *Org. Prep. Proced. Int*. **1986**, *18*, 299-327. c) Attanasi, O. A.; Filippone, P.; Serra-Zanetti, F. In *Trends in Heterocyclic Chemistry*, Menon, J., Ed.; Research Trends, Trivandrum, 1993; Vol. 3, pp. 461–479. d) Attanasi, O. A.; Filippone, P.; Serra-Zanetti, F. In *Progress in Heterocyclic Chemistry*, Suschitzky, H., Scriven, E. F. V., Eds.; Pergamon, Oxford, 1995; Vol. 7, pp. 1–20. e) Attanasi, O. A.; Filippone, P. In *Topics in Heterocyclic Chemistry*, Attanasi, O. A., Spinelli, D. , Eds.; Research Signpost, Trivandrum, 1996, Vol. 1, pp. 157–167. f) Attanasi, O. A.; Filippone, P. *Synlett* **1997**, *10*, 1128–1140. g) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *ARKIVOC* **2002**, *11*, 274-292.

[9] See SI for details of experimental procedure and optimization process.

[10] See books: (a) Begue, J. P.; Bonnet-Delpon, D. In *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, 2008. (b) *Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals*, Tressaud, A., Haufe, G., Eds.; Elsevier, Amsterdam, 2008. (c) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Petrov, V. A., Ed.; Wiley, Hoboken, 2009. (d) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*; Wiley-VCH, Weinheim, Germany, 2013. e) *Fluorine in Heterocyclic Chemistry*, Nenajdenko, V. G., Ed.; Springer, Berlin, 2014. (f) Prakash, R. V. *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, 2015.

[11] (a) Chattaway, F. D.; Bennett, R. *J. Chem. Soc*. **1927**, *11*, 2850-2853. (b) Chattaway, F. D.; Daldy, F. G. *J. Chem. Soc*. **1928**, 2756-2762. (c) Chattaway, F. D.; Browne, T. E. W. *J. Chem. Soc*. **1931**, 1088-1092. (d) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *Tetrahedron Lett*. **1995**, *36*, 5703-5706. e) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R. *Org. Lett*. **2009**, *11*, 309-312. (f) Gilchrist, T. L.; Parton, B.; Stevens, J. A. *Tetrahedron Lett*. **1981**, *22*, 1059-1062. (g) Gilchrist, L.; Stevens, J. A.; Parton, B. *J. Chem. Soc*. **1985**, 1741-1745. (h) Gilchrist, T. L.; Romero, O. A. S.; Wasson, R. C. *J. Chem. Soc*. **1989**, 353-359. (i) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem*. **1996**, *61*, 8921-8934. (j) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *Tetrahedron Lett*. **1996**, *37*, 1351-1355. (k) Baldoli, C.; Lattuada, L.; Licandro, E.; Maiorana, S.; Papagni, A. *J. Heterocycl. Chem*. **1989**, *26*, 241-244.

[12] See recent review Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed*. **2016**, *55*, 58-102.

[13] (a) Hudgens, J. W.; Johnson, R. D.; Tsai, B. P.; Kafaf, S. A. *J. Am. Chem. Soc*. **1990**, *112*, 5763-5775. (b) Robles, E. S. J.; Chen, P. *J. Phys. Chem*. **1994**, *98*, 6919-6923. (c) Andrews, L. *J. Chem. Phys*. **1968**, *48*, 972-979. (d) Rogers, E. E.; Abramowitz, S.; Jacox, M. E.; Milligan, D. E.; Hesse, C.; Leray, N.; Roncin, J. *J. Chem. Phys*. **1970**, *52*, 2198-2204.

[14] Zard, S. Z. *Chem. Soc. Rev*. **2008**, *37*, 1603-1618.

[15] For this type of radical cyclization in radical clock studies, see for example: (a) Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc*. **2014**, *136*, 17926-17929. (b) Parasram, M.; Chuentragool, P.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc*. **2016**, *138*, 6340-6343. (c) Liwosz, T. W.; Chemler, S. R. *Org. Lett*. **2013**, *15*, 3034-3037.

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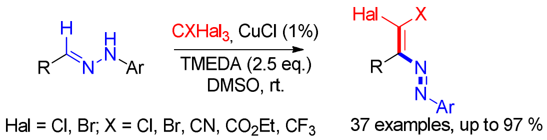
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CXHal$_3$, CuCl (1%)
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N
Ar
Hal = Cl, Br; X = Cl, Br, CN, CO$_2$Et, CF$_3$
37 examples, up to 97 %