C–C and C–Heteroatom Coupling

Copper-Catalyzed Direct Cross-Coupling of Compounds Containing Activated C–H/Heteroatom–H Bonds with N-Tosylhydrazones

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Abstract: Direct coupling between N-tosylhydrazones and various coupling partners such as 1,3-azoles, alkynes, and heteroatoms in the presence of Cu catalysts has turned out to be an extremely attractive route for carbon–carbon and carbon–heteroatom bond formation. Recently, both intra- and intermolecular versions, along with cascade reactions involving sequential inter- and intramolecular coupling, have made a significant impact in synthetic chemistry. Emphasis has been placed on copper as catalyst to highlight the advantages of these methods over those involving several other late-transition-metal catalysts. The limited advancements to date leave ample opportunity for further investigation in this area, which still has a long way to go in the near future. The key intermediates in these reactions arise from a carbene migratory insertion process that can be terminated in numerous ways, resulting in the formation of a diverse range of pharmaceutically important scaffolds.

Introduction

Synthetic organic chemistry has evolved to utilize various cross-coupling reactions for carbon–carbon and carbon–heteroatom bond formation by use of functionalized starting materials.[1] Generally, in most of these reactions, prefunctionalization of the raw material to obtain an active starting material is an additional reaction step. In this context, carbon–hydrogen and heteroatom–hydrogen bond activation are of tremendous potential because they offer the opportunity to avoid the prefunctionalization step either for both of the coupling partners or at least for one of the coupling partners (Figure 1).

![Figure 1. Strategies for carbon (sp³)–carbon/heteroatom bond formation.](image)

Moreover, the activation of a C(sp³)–H bond and its establishment as an active coupling partner remains challenging. In particular, the activation of C(sp³)–H bonds of secondary alkyl side chains is quite complex because it requires consideration of unwanted β-H elimination from the alkyl metal intermediate.[5] Very recently, transition-metal-catalyzed carbene transfer reactions from various aldehyde- or ketone-derived N-tosylhydrazones have emerged as an efficient synthetic methodology through which to address this problem.[6]

A more logical approach would be the integration of classical coupling reactions with the metal carbene process, implying the use either of a diazo compound or of a tosylhydrazine as one of the coupling partners, from which generate a reactive C(sp³) source after extrusion of nitrogen.[7] With this as a goal, the pioneering work of Van Vranken on Pd-catalyzed cross-coupling with diazo compounds as coupling partners has evolved as a new approach to C–C bond-forming reactions.[8] However, these coupling reactions were limited to stable diazo compounds such as (trimethylsilyl)diazomethane and α-diazo carbonyl compounds, whereas unstable diazo compounds without electron-withdrawing groups were found to be quite difficult...
to induce to react as coupling partners, thus limiting the reaction scope.

In another advancement, because N-tosylhydrazones are well-known to produce the corresponding unstable diazo compounds in situ, Barluenga and co-workers directly utilized hydrazones as a source of diazo compounds in Pd-catalyzed cross-coupling with various coupling partners, such as aryl halides, aryl triflates, aryl nonaflates, aryloboronic acids, and haloalkenes.[9]

However, direct coupling between N-tosylhydrazones and aryl or heteroaryl compounds in the presence of a transition-metal catalyst would be more concise and economical. Numerous Pd-catalyzed cross-coupling reactions of diazo compounds containing migratory groups such as aryl, vinyl, benzyl, acyl, allyl, allenyl, alkynyl, propargyl, and cyclopropyl have also been established.[10] It is reasonable to assume that other cheaper options for transition-metal-catalyzed coupling reactions still remain to be explored. Because of the easy availability, low cost, and low toxicity associated with copper salts and their side products, these reagents have been extensively used in many organic reactions and the topic has previously been reviewed by many authors.[11,12] Kozlowski and co-workers have overviewed Cu-catalyzed oxidations, functionalization, and coupling reactions under aerobic conditions.[11a] Yu and co-workers reported various highly efficient Cu-catalyzed C–H functionalization methods.[13] In the same year, Chatani and co-workers developed Cu-catalyzed C–H amination of 2-phenylpyridines.[14] Since these developments, increasing arrays of Cu-catalyzed C–H functionalization procedures involving organometallic mechanisms have been developed.[15a–5c] More recently, Stahl and co-workers summarized some current trends and mechanistic insights relating to Cu-catalyzed coupling reactions.[16] Mechanistically, copper(II) effectively yields an oxidative coupling product because it is a one-electron oxidant. Usually, a single electron is transferred from the electron-rich substrate, reducing CuI and thus initiating the reaction cascade.[17] Because copper can exist in multiple oxidation states the detailed mechanism of Cu-catalyzed C–H functionalization becomes quite intricate and cannot be generalized.

Although copper-catalyzed coupling reactions are well reviewed, surprisingly, Cu-catalyzed cross-coupling involving carbene migratory insertion processes is yet to be summarized. In the last five years, Cu-catalyzed carbene transfer has emerged as an efficient synthetic methodology for C–H activation. Rightly, it has attracted much attention from synthetic chemists, resulting in several reports on the development of effective methodologies. However, a critical review compiling all the available literature and future perspectives is still missing. This microreview focuses on recent updates relating to successful approaches to Cu-catalyzed direct cross-coupling be-

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between carbon(sp/sp³)–hydrogen or heteroatom–hydrogen systems and various N-tosylhydrazones. To aid the reader, the review is subdivided into carbon–carbon and carbon–heteroatom bond-formation processes.

1. Carbon–Carbon Bond Formation

Even after significant progress to date, Cu-catalyzed cross-coupling with tosylhydrazones is mostly limited to C(sp)–H and C(sp²)–H systems as coupling partners. The reaction mechanism is assumed to proceed through Cu-catalyzed C–H activation as the initial step, followed by migratory carbene insertion (Figure 2). It is observed that reactions of electron-deficient C–H bonds are favored. The mechanism also seems to follow a route complementary to the classical electrophilic sp² C–H insertion process, in which the transition metal first activates the tosylhydrazone counterpart to form the metal carbene, followed by C–H insertion.

(a) Coupling Between C(sp)–H Systems and N-Tosylhydrazones

Coupling between C(sp)–H systems and N-tosylhydrazones has mainly been reported in the context of the synthesis of pharmaceutically important allene cores as intermediates or final products. Apart from that, this approach leading to formation of ethynylation products can also be a viable alternative to Sonogashira reactions. Palladium chemistry with N-tosylhydrazones as substrates and halides as coupling partners has recently garnered a lot of attention, because palladium-catalyzed cross-coupling involving Pd carbenes and subsequent migratory insertion has been shown to be highly efficient and versatile. In contrast, the exploration of copper-catalyzed reaction conditions still has a long way to go. To this end, Wang and coworkers recently reported efficient copper(I)-catalyzed cross-coupling between N-tosylhydrazones and terminal alkynes, mostly yielding trisubstituted allenes. As an extension of the methodology the same group explored it and incorporated minor modifications for the formation of disubstituted terminal allenes.

At the outset of the investigation, several sets of reaction conditions were tried, and the most effective conditions emerged when N-tosylhydrazones 1 (1.3 equiv.) were treated with phenylacetylene (1 equiv.) in the presence of Cu(MeCN)₄PF₆ (5 mol-%) and ligand L (6 mol-%) with cesium carbonate (3 equiv.) as base in dioxane (3 mL). The desired allene 3a was obtained in 87 % yield (Scheme 1). The most efficient reaction conditions identified by the screening process and the substrate scope were further explored with various terminal alkynes and N-tosylhydrazones. It was noted that the ligand-promoted (L-promoted) copper-catalyzed coupling be-
tween N-tosylhydrazones 1 and various terminal alkynes 2 yielded the corresponding coupled products 3a–j in synthetically viable yields (Scheme 1). Interestingly, similar yields were observed for both electron-releasing (3e and 3g) and electron-withdrawing aromatic substituents containing alkyne groups (3b and 3d), and that varying the aromatic ring substituents had no significant effect on the yields. A lower yield was observed in the case of a p-CF₃ (compound 3c) substituent on the terminal alkyne-aryl ring. It was further demonstrated that the reaction was well tolerated with naphthyl-substituted alkynes 3f and 3g, although use either of a nitro-substituted arylhydrazone or of the hydrazone derived from /βα-phenylacetaldehyde reduced the yields of corresponding products 3i and 3j.

Later, the same group carried out three-component reactions with N-tosylhydrazones 4, terminal alkynes 5, and allyl halides 6; these represent an efficient route to the synthesis of tri- and tetrasubstituted allenes (Scheme 2). The CuI-catalyzed sequential reaction of N-tosylhydrazone, phenylacetylene, and allyl iodide in dioxane at 90 °C was examined as the initial phase of optimization. Further, use of the phase-transfer catalyst TBAB helped in enhancing the yield of the reaction. The reaction was also performed with an excess of NaH, which helps in trapping the proton more efficiently, because protonation was found to be easier than nucleophilic attack on the allyl halide. Finally, the maximum yield of the allene product 7a was obtained with use of 20 mol-% of Cu, 6 equiv. of sodium hydride, and 20 mol-% of TBAB as phase-transfer catalyst in dioxane at 90 °C.

With the optimized reaction conditions to hand, the substrate scope of this reaction was explored by using various substituted aldehyde-derived N-tosylhydrazones, terminal alkynes, and allyl halides. N-Tosylhydrazones and terminal alkynes with either electron-donating or electron-withdrawing groups worked well, affording products 7a–i in moderate to high yields. With N-tosylhydrazones derived from ketones the reaction conditions required certain changes, such as the use of 20 mol-% of [Cu(MeCN)₄]PF₆ instead of Cul, 5 equiv. of sodium hydride, and an increase in the temperature from 90 °C to 110 °C to provide good yields of the products 7j and 7k.

Recently a viable alternative to the Sonogashira reaction at a saturated center, based on C(sp³)–C(sp) coupling, has been introduced by Wang et al. The synthetic approach to this through the incorporation of alkyl moieties by use of functionalized alkyl precursors has always been a challenge. The newly developed CuI-catalyzed cross-coupling of N-tosylhydrazones 8 and trialkylsilylethynes 9 to yield ethynylated products 10 provided a new approach to solving the existing problem relating to the attachment of an alkyne moiety to the saturated center (Scheme 3) and since its development has become a commonly used method for the construction of C(sp)–C(sp³) bonds. During optimization of the reaction conditions, use of the substrates N-tosylhydrazone 8a and ethynyltrimethylsilane (9) afforded the alkyne product 10a in maximum yield of 75 % (Scheme 3).

Next, the scope of the various N-tosylhydrazones 8a–m, derived from aromatic aldehydes and ketones, under the optimized conditions was explored. The cross-coupling process was found to be efficient and tolerant to a series of diversely functionalized substrates containing electron-releasing or electron-withdrawing groups. Also, the cross-coupling was found to be tolerant to N-tosylhydrazones 8n–p, derived from aliphatic aldehydes.

Mechanistically, it was proposed by Wang et al. that both the reactions proceed through the cross-coupling giving rise to the formation of a common allene intermediate. This is followed by 6π-electron cyclization/isomerization, affording the phenanthrene derivatives 15 in moderate to good yields.

Fluorinated 1,3-enynes are regarded as the most versatile precursors of organofluorine compounds. However these have to date been less widely explored than non-fluorinated 1,3-enynes. The classical methods in this area demand either the existence of leaving groups on alkynes or the use of dual-metal systems. In contrast, an alternative approach involving easy installation of the fluorinated component onto an alkyne through C–H functionalization with the N-tosylhydrazone satisfies this long-desired goal. In this context, a more recent report on Cu-catalyzed C(sp^3)–C(sp^3) bond formation followed by β-fluoro elimination was made by Jinabo Wang. In the process
of optimization of the reaction conditions, the model substrates phenylacetylene (16a) and N-tosylhydrazone 17a (1:1 ratio) were treated with CuI (20 mol-%), LiOrBu (2.0 equiv.), LiOTf (1.0 equiv.), and TBAC (20 mol-%) in dioxane at 60 °C for 2 h to afford 1,1-difluoro-1,3-ene 18a in 71 % yield (Scheme 5). The substrate scope was verified by altering the substituents either in the alkyne or in the N-tosylhydrazone to achieve the corresponding 1,1-difluoro-1,3-ene derivatives 18a–o in moderate to good yields. There is no significant variation in the yields of the products arising from the substituent diversification. However, a low yield of the desired product 18i was obtained when thiophenyl-substituted N-tosylhydrazone 17i was introduced as substrate. The variation of substituents in the alkyne component also proved compatible with the reaction conditions, providing good yields of products 18l–n except in the case of the cyclohexenyl-substituted alkyne 16e, in which the yield of 18o was found to be as low as 49 %.

The highly versatile ligand-free CuBr-catalyzed coupling/cyclization has been further used by Wang and co-workers to synthesize benzofurans and indoles. Needless to mention, economical methods to synthesize these moieties, which frequently occur in many natural products,[27] have attracted great attention.[28] Wang and co-workers coupled terminal alkynes 20 with N-tosylhydrazones 19, derived from o-hydroxy- or o-aminobenzaldehydes, to yield products 21 (Scheme 6).[29] The procedure was optimized after screening of a sequence of reaction conditions by variation of various reaction parameters. The most effective reaction conditions were achieved with CuBr (10 mol-%) and Cs2CO3 (3 equiv.) in acetonitrile. These reaction conditions were tolerated by many substituents, including various aryl, alkyl, naphthyl, and heterocycle groups, present in the alkyne components 20a–h. The variation of substituents on the aromatic rings of the terminal alkynes; both electron-rich and electron-deficient aryl-substituted alkynes 20b–d were effective. Moreover, treatment of heteroaryl- and alkyl-substituted alkynes with N-tosylhydrazones of o-aminobenzaldehydes furnished the indole derivatives 21g and 21h in 72 % and 41 % yields.

All the above reactions proceed through similar mechanistic pathways in which common intermediates of type E, generated through a copper carbene migratory insertion process, have been proposed as the key intermediates for all the products. The fate of the Cu complex E can involve five different pathways – i, ii, iii, iv, and v – including quenching with allyl iodide, protonation, reductive elimination, β-fluoride elimination, or intramolecular addition of a heteroatom to an allene intermediate, leading to structurally diversified products P1–P5 (Figure 3). In all cases (pathways i, ii, and v) allenes were obtained as intermediates or products, except for the cases of reactions in which trifluoromethyl-substituted N-tosylhydrazones (pathway iii) or silyl-substituted alkynes (pathway iv) were used as one of the coupling partners. It was observed that in the case of trifluoromethyl-substituted N-tosylhydrazones, β-fluoride...
elimination competes with and predominates over the possibility of formation of allenes.

**Figure 3.** The common plausible mechanistic approach.

(b) Coupling Between C(sp²)–H Systems and N-Tosylhydrazones

Intermolecular coupling between C(sp²)–H systems and N-tosylhydrazones is mainly directed towards the functionalization of 1,3-azoles, N-iminopyridinium ylides, and polyfluoroarenes. Functionalized 1,3-azoles constitute an important class of heteroaromatics due to their frequent occurrence in pharmaceutically important compounds, natural products, and functional materials.[30] In particular, 2-substituted azoles are important because of their very high biological activities. For instance, 2-alkylbenzimidazole systems are known not only for their antihyperglycemic activity, anti-hepatitis B virus (HBV) activity, and as AMP-activated protein kinase (AMPK) activators (crucial for obesity) but also for their potential as therapeutic agents for chronic heart failure (5-HT₂B antagonists) and as neprilysin inhibitors for lowering blood pressure.[31] Thus, synthetic endeavors to produce heteroarenes with pertinent substitution have seen strong growth.[32] 1,3-Azoles with acidic C–H bonds (pKₐ range 24–27) resembling those of terminal alkynes can be coupled with N-tosylhydrazones.

In 2010, Wang and co-workers reported direct benzylation or allylation of 1,3-azoles 22 by treatment with N-tosylhydrazones 23 in the presence of CuI as a catalyst. Here, N-tosylhydrazones act as "masked" carbenic moieties.[33] The use of 10 mol-% CuI in the presence of LiOrBu as the base in toluene at 110 °C was described (Scheme 7). The procedure was extended to benzylation of benoxazoles, 5-phenylbenzoxazoles, benzthiazole, and 4,5-dimethylthiazole with various aryl N-tosylhydrazones, affording products 24a–h in moderate to good yields. During exploration of the substrate scope it was observed that

![Scheme 7. Direct benzylation of azoles with N-tosylhydrazones.](image-url)
the reaction was well tolerated both by electron-withdrawing and by electron-donating groups on the aromatic rings of the N-tosylhydrazones 23a and 23b. These optimized reaction conditions were also screened for direct alkylation. Coupling of the 3-methylcyclohex-2-enone-derived N-tosylhydrazone to benzoxazole required a slightly increased loading of the CuI (20 mol%), affording the desired product 24d in 62% yield.

In view of oxazole’s reactivity in this coupling procedure, thiiazoles were also screened for benzylaion. For these, coupling with various N-tosylhydrazones in the presence of 20 mol-% of CuI in dioxane as solvent gave moderate to high yields of 24e–h. The need for higher catalyst loadings for the thiiazoles than for oxazoles is due to the lower acidity of C–H bonds of thiiazoles.

Synthesis of ferrocene-derived ligands, which have extensive applications in organic chemistry, has received limited attention. In one attempt in this direction, Zhang et al. prepared differently functionalized ferrocenyl moieties through copper-catalyzed cross-coupling between ferrocene-derived N-tosylhydrazones and benzo[d]oxazoles. CuBr-catalyzed C–H bond functionalization of 1,3-azoles 22 either with N-tosylhydrazones 25, derived from ferrocenyl alkyl ketones, or with N-tosylhydrazones 26, derived from 1,1′-ferrocenyl diketones, was reported (Scheme 8).[34] LiOrBu was successfully employed as the base in toluene at 120 °C with CuBr as the catalyst. A rich range of ferrocenyl alkyl ketone groups or ferrocenyl aryl ketone groups underwent smooth coupling with 1,3-benzo[d]oxazoles irrespective of steric hindrance (compounds 27a–c). Various substituted benzo[d]oxazoles could also be coupled without any loss in yield (compounds 27d and 27e). In addition, benzo[d]-thiazole was also found to be suitable coupling partner, giving 27f.

Modification of reaction conditions by raising the amounts of catalyst and base for coupling between similar oxazoles/thiazoles and N-tosylhydrazones derived from 1,1′-ferrocenyl diketones proved equally significant. Various substituted 1,1′-ferrocenyl-diketone-derived N-tosylhydrazones were found to be viable substrates for coupling with substituted benzo[d]oxazoles and benzo[d]thiazoles under optimized conditions (compounds 28a–c).

In light of the occurrence and utility of oxadiazole systems in medicinal and materials science, the construction of particularly

Scheme 8. Cross-coupling of ferrocenyl-ketone- and 1,1′-ferrocenyl-diketone-derived N-tosylhydrazones with various 1,3-azoles.
substituted oxadiazoles has always been synthetically attractive. In 2013, Das and co-workers applied the strategy of copper-catalyzed C–H activation of 1,3-azoles by using N-tosylhydrazones for direct benzylation of 1,3,4-oxadiazoles (Scheme 9).[35]

Use of catalytic copper iodide (5 mol-%) and Cs2CO3 (2.5 equiv.) in toluene was found to be the optimized condition for coupling between 2-phenyl-1,3,4-oxadiazole derivatives 29 and N-tosylhydrazones 30, to give the corresponding benzylated oxadiazole derivatives 31. Surprisingly, use of LiOttBu and K3PO4 reduced the efficiency of the reaction drastically. The reaction was extended to direct benzylation and alkylation of 2-phenyl-1,3,4-oxadiazole with different N-tosylhydrazones, and excellent yields of 31a–c were observed in these cases. However, the coupling did not proceed with N-tosylhydrazones derived from aldehydes. A broad range of oxadiazoles containing both aromatic and heteroaromatic moieties with different substituents (electronic-withdrawing and electronic-donating) at the C-2 position were coupled effectively with N-tosylhydrazones to afford 31d–f. 1,3,4-Oxadiazoles bearing aliphatic substituents did not undergo the coupling reaction, due to their low reactivity.

To elicit the mechanistic pathway of C–H secondary alkylation, various control experiments were run by Wang. It is proposed that the key step in the reaction is the migratory insertion of Cu carbene species to give a species of type I (Figure 4). However, the possibility of direct Cu carbene insertion into a heterocycle C–H bond by a concerted reaction pathway could not be strictly eliminated. Thus, further thorough studies to provide detailed mechanistic insight into these reactions are needed. Also, in the elucidation of the mechanism certain ambiguities associated with initial metal insertion steps need to be carefully addressed.

In order to clarify the discrepancies associated with the mechanistic interpretation, Wang et al. investigated (i) variation in equivalents of base needed to convert N-tosylhydrazones into diazo compounds, (ii) the role of base, (iii) kinetic isotope effects, by exchange of azole C2–H with deuterium, and (iv) effects of lower electron density of azoles, relative to electron-rich heterocycles such as indoles and pyrroles, on the reaction. However, these observations eliminated the possibility of metal carbene insertion into the C–H bond in a direct pathway. Hence, a mechanism involving a metal carbene migratory insertion process appeared more likely. Thus, it is proposed that the N-tosylhydrazone S2 yields the diazo substrate in the presence of a base, and that this reacts with the metal azole intermediate G to generate the metal carbene species H. This is followed by migratory insertion of the heteroaryl group on the metal to the carbenic carbon atom, affording metal species I. Protonation of I would provide the desired alkylated product P6 (Figure 4).

Wang and co-workers revealed a method for copper-catalyzed regioselective ortho-C–H bond activation of N-iminopyridinium ylides (Scheme 10).[36] The sole purpose of the N-iminopyridinium system was to provide control over regioselectivity.
optimum reaction conditions were achieved with treatment of N-tosylhydrazones 33 with N-iminopyridinium ylides 32 in the presence of 20 mol-% Cul and 3.5 equiv. of LiO\textsubscript{t}Bu as base in toluene. The copper catalyst and base generate a cyclic Cu\textsuperscript{i} pyridinium ylide intermediate leading to the initiation of the reaction by direct C–H bond activation. The thus-formed cyclic intermediate undergoes copper carbene formation with the diazo derivative generated in situ. Further, a migratory insertion and protonation result in the products 34a–g. All the products were obtained in good to excellent yields. The scope and limitations of the reaction with N-iminopyridinium ylides and N-tosylhydrazones were investigated further. The reaction was practically unaffected by variation of substituents on the tosylhydrazones. Finally, it is noteworthy that in none of the cases 2,6-dialkylated product could be detected.

More recently, the alkylation of polyfluoroarenes, F-containing compounds with wide application, following a similar Cu\textsuperscript{i}-catalyzed C–H bond-activation approach has also been explored (Scheme 11).

Alternative approaches for the alkylation of polyfluoroarenes that have successively emerged in last few years compete with the upcoming Cu-catalyzed methodology. Notably, the development of Cu\textsuperscript{i}-carbene-based migratory insertion of polyfluoroarenes has become the most efficient and simple method addressing the challenges associated with the alkylation of polyfluoroarenes. 1,2,4,5-Tetrafluorobenzene (35a) and N-tosylhydrazone 36a were introduced as model substrates for the optimization of the reaction conditions.

With 20 mol-% Cul, 3 equiv. of LiO\textsubscript{t}Bu, and 20 mol-% of 1,10-phenanthroline in 1,4-dioxane/acetonitrile (1:1) the reaction gave the maximum yield (74 %) of the expected alkylation product 37a. As for the substrate scope, N-tosylhydrazones with electron-donating groups on the aromatic ring gave higher yields, albeit not significantly, than those with electron-withdrawing groups (compounds 37b–g). However, fairly moderate yields were observed with halogen substituents (compounds 37e–g).

N-Tosylhydrazones derived from cyclic ketones also worked well in this reaction, to give 37h and 37i. Other variation in the polyfluoroarene counterpart also afforded moderate to good yields of the desired products 37j and 37k. Although direct access to substituted polyfluoroarenes was achieved, the reaction efficiency was found to be pronounced only with heteroaromatic or polyfluoroarene substrates.
2. Carbon–Heteroatom Bond Formation

In this class of Cu-catalyzed cross-coupling with tosylhydrazones, recently N–H and P–H activation have been reported. The mechanism of the carbon–heteroatom bond formation is believed to involve the generation of a metal carbene J in the initial step, in contrast with carbon–carbon bond formation, in which metal-catalyzed C–H activation is the initial step. The metal carbene is further terminated by insertion into a heteroatom–hydrogen bond, leading to an intermediate K, followed by protonation or cascade reactions (Figure 5).

![Figure 5. Plausible mechanism for carbon–heteroatom bond formation.](image)

(a) Coupling Between N–H Systems and N-Tosylhydrazones

A few years ago, Hamze and Alami came up with a simple and efficient protocol for direct copper-catalyzed reductive coupling between N-tosylhydrazones and amines in the presence of a base (Scheme 12). In the initial reaction, a variety of arylsulfonyl hydrazones 38 were treated with primary and secondary aliphatic amines 39, yielding aryl- and diarylmethylamine derivatives 40a-f in practically useful yields. The optimized reaction condition obtained by coupling N-tosylhydrazone 38a with the secondary amine 39a in the presence of Cu(acac)2 and Cs2CO3 in dioxane was further implemented on several substrates. A series of hydrazones 38a-f were coupled with various amines, including azole derivatives, under the optimized reaction condition.

![Scheme 12. Cross-coupling between N-tosylhydrazones and amines.](image)

In later years, Y. Zhang and co-workers developed Cu-catalyzed annulation of N-tosylhydrazones with primary amines through C–N and N–N bond formation to form 1,2,3-triazoles. Later, as an extension of reductive coupling between N-tosylhydrazones and amines, Aziz and Hamze revealed an unprecedented copper-catalyzed sequential addition of a C(sp3)–N bond followed by a C(sp3)–C(sp2) bond on the same N-tosylhydrazone carbenic center (Scheme 13). The method involves a cascade reaction sequence starting from a 2-halo-biarylhydrazone, leading to a straightforward synthesis of 9H-fluoren-9-amine derivatives, which are otherwise not that easy to achieve. After recognition of the underlying challenges asso-

ciated with the synthesis of 9H-fluoren-9-amine derivatives,[41] the uniqueness of the developed methodology for their synthesis was identified. Moreover, the unexpected intermolecular C–N bond-forming reaction followed by an intramolecular C–C bond-forming reaction at the same carbenic center encouraged further exploration of methodological investigations. Evaluation of various reaction parameters established that Cu(acac)2 (10 mol-%) and Na2CO3 (2.5 equiv.) in glycerol at 80 °C gave the best isolated yield (62 %) of the desired product N-(4-methoxyphenyl)-9H-fluoren-9-amine (43a). The feasibility of this coupling was demonstrated with different types of amines 42 and 2′-bromo-biphenylhydrazones 41. In all cases, 9H-fluoren-9-amine derivatives were obtained in moderate to good yields irrespective of the substitution in the amine component.

The mechanistic insight into the reaction forming both a C–N bond and a C–C bond on the same carbenic center was provided by Hamze and co-workers and is illustrated in Figure 6. It was proposed that in the presence of the diazo compound and glycerol, the reaction proceeds with the reduction of copper(II) to catalytically active copper(I). Further, the copper(I) species reacts with the diazo compound, which is generated by the decomposition of N-tosylhydrazone S3 under basic conditions, to yield L. The electrophilic copper carbene L can then generate ylide M through a nucleophilic addition of the amine. The fate of M can be either a 1,2 proton shift or the generation of copper(III) intermediate N through an intramolecular oxidative addition of the ylide. It is hypothesized that under the reaction conditions, instead of a 1,2 proton shift usually favored in a protic medium, leading to N–H insertion, the formation of copper(III) intermediate N predominates. The thus-generated intermediate N can undergo reductive elimination followed by deprotonation, leading to the product P7 and regeneration of the catalytic CuI species.

Organophosphorus compounds are of great importance not only in organic chemistry but also in materials synthesis, catalysis, and biochemistry. This vast range of applications prompts researchers to explore new approaches for the construction of C–P bonds. Wu Lei and co-workers developed a new method for C(sp3)–P bond formation through copper-catalyzed reductive coupling between N-tosylhydrazones and H-phosphorus oxides (Scheme 14).[42] The reaction between 1-[1-(4-methoxyphenyl)ethylidene]-2-tosylhydrazone (44a) and diphenylphosphine oxide (45a) in dioxane in the presence of CuCl2 (20 mol-%) and excess K2CO3 (3 equiv.) as base afforded the coupled products 46a-f in moderate to good yields.

product 46a in 80 % yield. Various substituted N-tosylhydrazones 44 were synthesized as substrates in order to confirm the generality of the method. It was observed that the presence either of an electron-rich or of an electron-deficient aryl substituent on the N-tosylhydrazone yielded the corresponding compound (46a or 46b) in good yield. In some cases (product 46d) in which the yields were unsatisfactory, DMF was found to be a better solvent to improve the yield; however, this is not general for all substrates.

Conclusion

Direct cross-coupling between N-tosylhydrazones and C(sp³)-H, C(sp)-H, or heteroatom–H groups represents a method with great potential for the synthesis of an array of pharmaceutically important compounds through the construction of carbon–carbon and carbon–heteroatom bonds. Furthermore, the use of inexpensive and bench-stable copper salts makes it even more attractive. Still, several challenges such as broadening of substrate scope and acquisition of more in-depth mechanistic insight need to be addressed.

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