University of Tartu
Faculty of Physics and Chemistry
Institute of Organic and Bioorganic Chemistry

Pavel Starkov

Application of Azomethine and Azo Compounds in the Synthesis of Nitrogen-Containing Compounds

Master's Thesis in Organic Chemistry

Supervisor:
Uno Mäeorg, PhD

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Contents

Abbreviations

Substituents/protecting groups: Ac – acetyl, acac – acetylacetonate, All – allyl, Alloc – alloloxycarbonyl, Alk – alkyl, An – anisyl, Ar – aryl, Bn – benzyl, Boc – *tert*-butyloxycarbonyl, Bu – butyl, Cbs – *para*-cyanobenzosulfonyl, Cbz – benzyloxycarbonyl, Et – ethyl, Fmoc – 9-fluorenylmethoxycarbonyl, Me – methyl, Np – naphthyl, Ph – phenyl, Piv – pivaloyl, Pr – propyl, Tf – triflate, TMS – trimethylsilyl, Tol – tolyl, Tos – tosyl

Reagents/solvents: DBAD – di-*tert*-butyl azodicarboxylate, DCE – 1,2-dichloroethane, DCM – dichloromethane, DMA – dimethylacetamide, DMAE – 2-dimethylaminoethanol, DMAP – *N,N´* – dimethylaminopyridine, DMF – dimethylformamide, DO – dioxane, NBS – *N*-bromosuktsiinimiid, NMP – *N*-methylpyridine, Pro – proline, RAMP – (*R*)-1-amino-2-(methoxymethyl)pyrrolidine, SAMP – (*S*)-1-amino-2-(methoxymethyl)pyrrolidine, TEA – triethylamine, TFA – trifluoroacetic acid, THF – tetrahydrofurane, TMEDA – *N,N,N´,N´*-tetramethylethylenediamine, TMS – tetramethylsilane

General: Δ – heating, IR – infrared spectroscopy, MALDI – matrix assisted laser desorption ionisation, mp – melting point, MS – mass spectrometry, NMR – nuclear magnetic resonance spectroscopy, rt –room temperature, UV – ultraviolet spectroscopy

Introduction

The derivatives of hydrazine were discovered before hydrazine itself was identified in the late 19th century. By now, a great number of hydrazine derivatives are used as precursors for the construction of nitrogen-containing heterocycles, as leads in medicinal chemistry not mentioning the application of hydrazines in analytical chemistry and peptidomimetics. Since several mild and chemoselective nitrogen-nitrogen bond cleavage methods were developed, hydrazine derivatives are utilised in the asymmetric synthesis of amines and amino acids. The extensive research in carbon-nitrogen bond formation is the *raison d'être* for the present study of application of known and development of new synthetic methodologies for hydrazine derivatisation.

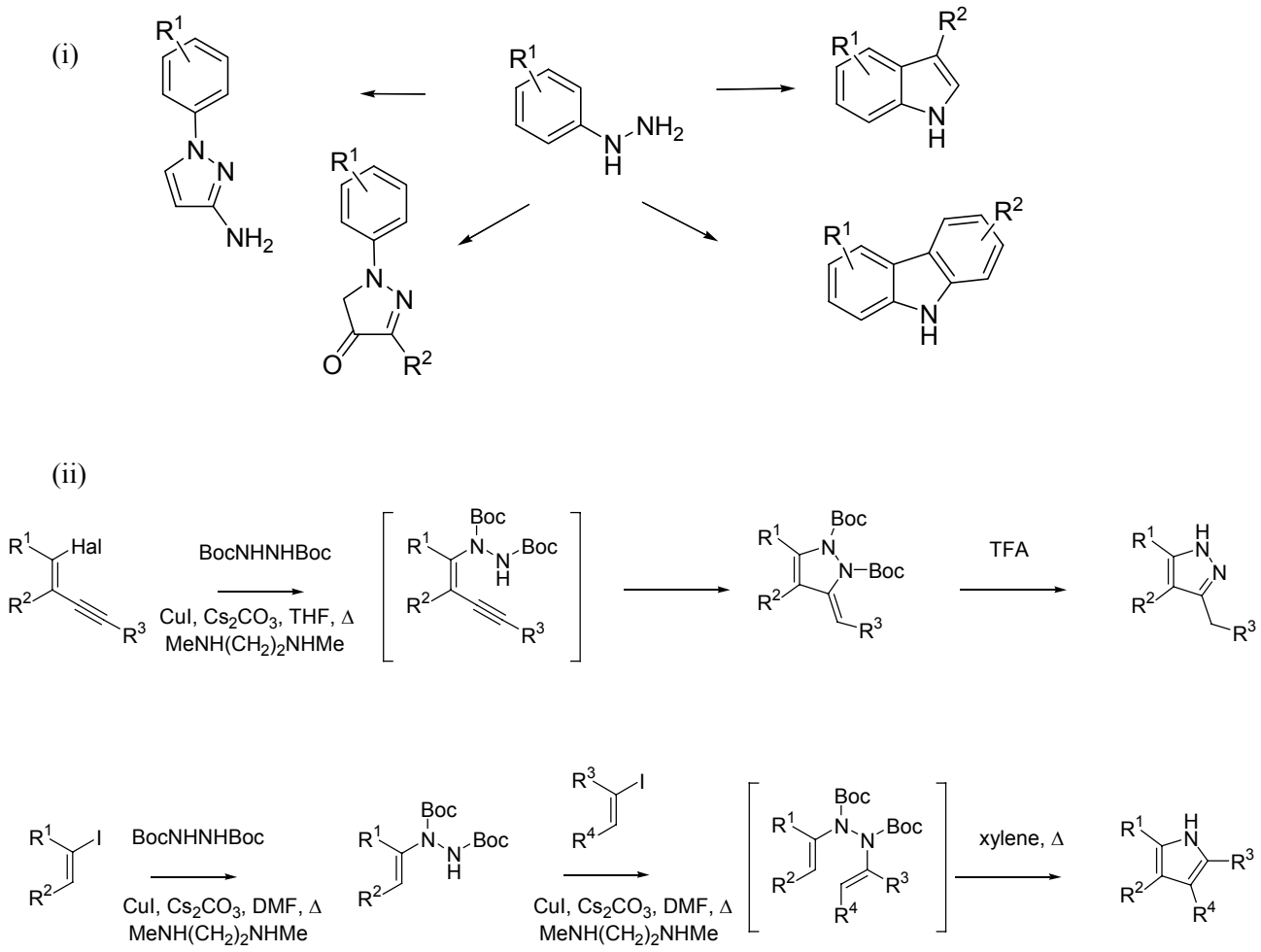
In this thesis one will find *(a)* a comparative study of copper-catalysed *N*-arylation of carbamate protected hydrazones with organobismuthanes and arylboronic acids, studies *towards (b)* electrophilic amination of terminal acetylenes and *(c)* proline-catalysed organocatalytic synthesis of β-hydrazino carbonyl derivatives with hydrazones as potential electrophiles.

Literature Overview

1.1 Hydrazine Chemistry

Hydrazines [1] are useful in a number of ways and their applications are summarised below:

(a) construction of heterocycles [2] (several examples are shown in Scheme **1**);



Scheme 1 Synthesis of heterocycles: (i) synthetic utility of arylhydrazines, (ii) recent syntheses of highly substituted pyrazoles [2g] and pyrrols [2h]

(b) peptidomimetics as azapeptides and azatides (Figure **1**) [3]

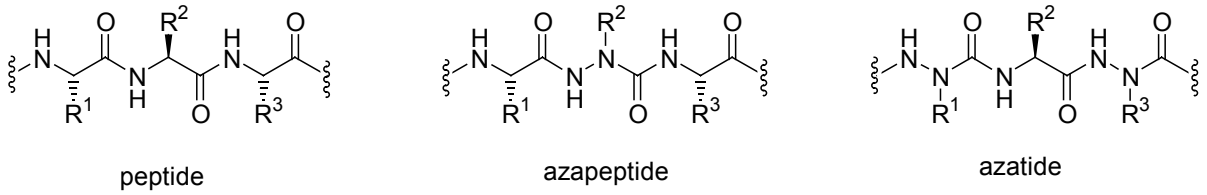
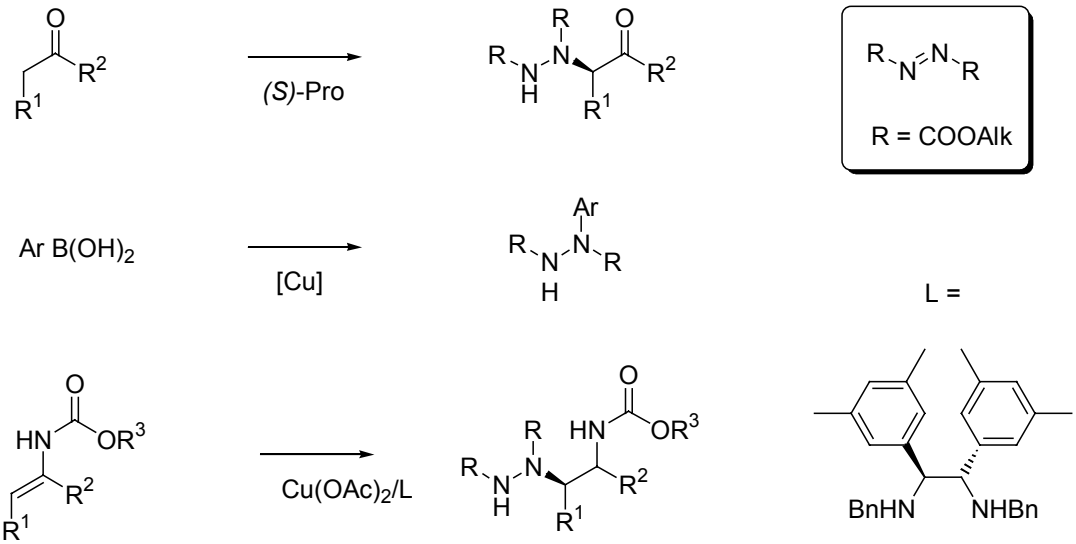


Figure 1 Azapeptides and azatides as peptide mimetics

(c) reagents in organic synthesis (hydrogen acceptor in Mitsunobu reaction [4]; SAMP/RAMP and relative methodologies [5]; Wolff-Kischner reduction of carbonyl groups [6], recently improved by Myers [7], Hartwig synthesis of aryl ketones [8]);

(d) electrophilic aminative agents (α-hydrazination of carbonyl compounds [9], amination of boronic acids [10], amination of encarbamates leading to orthogonally protected 1,2-diamines [11] are shown in Scheme **2**);



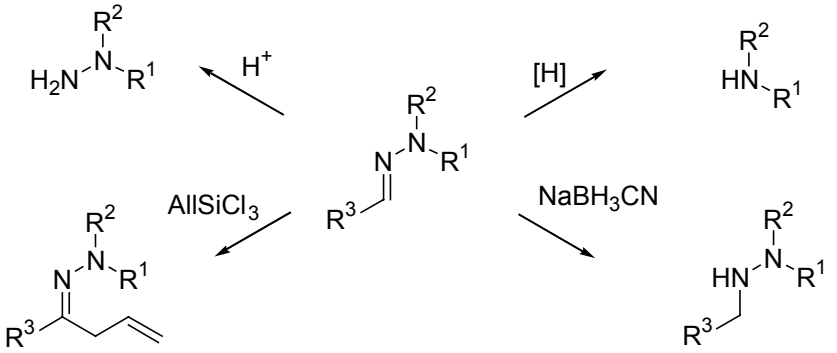
Scheme 2 Dialkyl azodicarboxylates in electrophilic amination

(e) pharmaceuticals [12] and pesticides [13];

(f) molecular electronics [14];

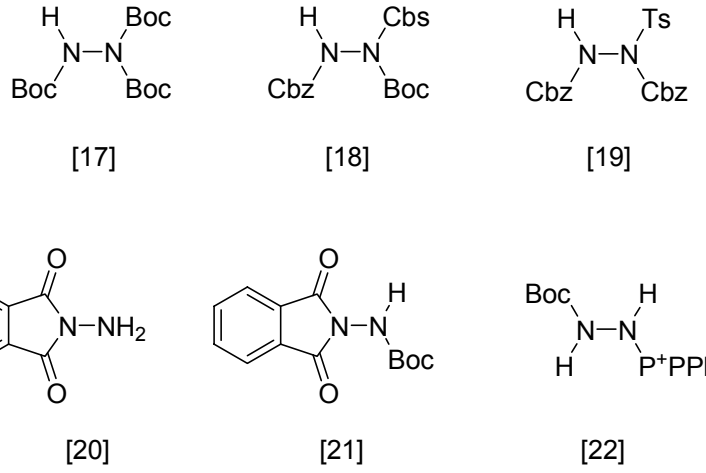
(g) reagents in analytical chemistry [15];

(h) additionally due to the greater stability of hydrazones compared to imines, the former are gaining popularity both in synthesis (Scheme **3**) and applications [16].



Scheme 3 Synthetic utility of hydrazones

Thus, the greater interest seen in the past decade is putting pressure on the development of new synthetic methodologies and application of already known for the derivatisation of hydrazines. Depending on chemical properties of the moiety to be introduced, different synthetic strategies are applied. However, most of them make use of orthogonally substituted precursors (Scheme **4**) [17-22]. In addition, one has to aim at more convenient, simpler and "atom-economic" [23] methods that run under mild conditions.



Scheme 4 Orthogonally substituted hydrazine precursors

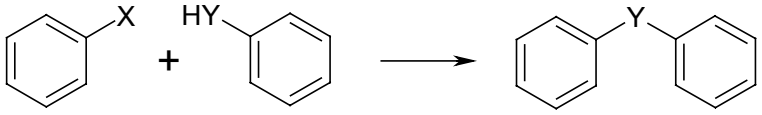
Further in Chapter **1**, the material that is relevant to the present thesis will be reviewed.

1.2 Metal-Catalysed Aryl Carbon–Nitrogen Bond Formation

The carbon-nitrogen bond formation is highly exploited in organic synthesis. As shown in the recent review of reactions used in pharmaceutical industry, *C*-heteroatom bond formation *via*

arylation or alkylation comes first with 19% of all reactions [24]. Among heteroatoms nitrogen is the most popular with 57% [24].

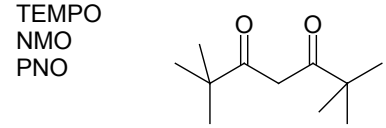
At the present time *N*-arylation is achieved by copper [25], nickel [26] and palladium [27] catalysis. Among these three, nickel is hardly used since much less work has been done on it and the results seem to be less promising compared to copper and palladium-based methods. Although the palladium chemistry and especially palladium-catalysed arylation received a lot of attention in the past two decades, palladium is expensive, requires harsh (high temperature and the use of strong base) and optimised reaction conditions, makes use of sophisticated ligands, is highly moisture and/or air-sensitive and, last but not least, is toxic.



X = $B(OR)_2$, Cl, Br, I, OTs, OTf, $BiAr_2$, $I^+ArBF_4^-$, $BiAr_2X_2$, $Pb(OAc)_3$, $Si(OMe)_3$, $BF_4^- K^+$

Y = NH, O, S

Cu sourse	***Solvent***	***Base***	***Oxidant***	***Other Additive***
Cu bronze	DCE	CsOAc	Air	Molecular sieves
CuI	DCM	K_2CO_3	Oxygen	cat H_2O
CuCl	DO	Na_2CO_3	TEMPO	
CuBr	DMA	K_3PO_4	NMO	
CuOAc	DMF	Cs_2CO_3	PNO	
$Cu(OAc)_2$	Toluene	t-BuOK		
$Cu(OPiv)_2$	Xylene	t-BuONa		
$Cu(acac)_2$	NMP	TEA		
$CuPF_6(MeCN)_4$	i-PrOH	Py		
$[Cu(OH)TMEDA]_2Cl_2$	MeOH	DMAP		
$(CuOTf)_2\ C_6H_6$	THF	phen		



Selected "solubilising" ligands

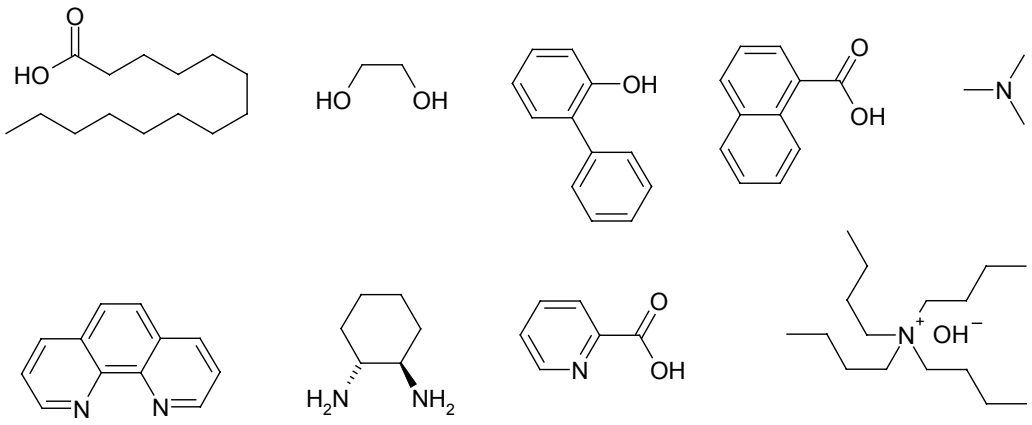


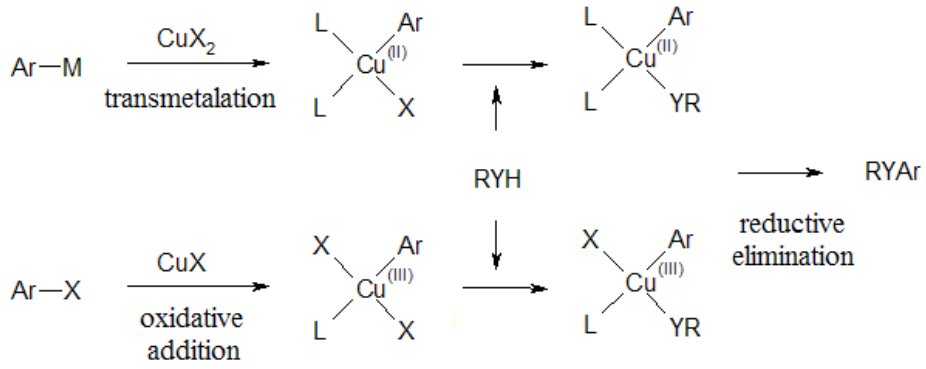
Figure 2 Copper-catalysed arylation

Copper-catalysed methods (Figure **2**) introduced more than a century ago by Ullmann and Goldberg have undergone a so-called copper *renaissance.* Extensive research led to significantly milder reaction conditions and lower copper loadings [24a]. A variety of *C*-, *N*-, *O*- and *S*-arylation can be carried out with various aryl donors: aryl halides, arylboronic acids, aryl iodonium salts, organobismuthanes, aryllead(IV) triacetates, arylstannanes, aryl trifluoroborate salts and arylsiloxanes.

The copper-mediated coupling of amines with aryl iodides and triflates is carried out under heating, but it requires weak not strong bases. Additionally, even less reactive bromides and chlorides were reported to afford the desired products. However, the amination of amides and heterocycles with aryl halides was mostly inefficient compared to amines until Buchwald and others optimised the original Goldberg conditions of amidation of aryl halides by adding *N*,*N'*-dimethyl-1,2-diamines or amino acids to give enhanced reactivities and better yields though the reaction is still to be carried out at elevated temperatures [28]. Both arylbsoronic acids and organobismuthanes were reported to arylate substrates (aryl halides, amines) under much milder conditions (rt, weak base) [29, 30].

The general mechanism of copper-catalysed arylations is analogical to other metal-catalysed couplings with oxidative addition and reductive elimination as crucial steps. The exact mechanism depends on aryl donor and copper source (Scheme **5**). Cu(III) is largely believed to be involved and the participation of organocopper(III) species was recently proved by rapid injection-NMR [31]. The oxidation state of the metal also depends on reaction conditions, oxidative agents (e.g. TEMPO, air) as additives in particular. For arylboronic acids, oxidative conditions enhance the process at the expense of higher loadings of arylboronic acid, because they undergo oxidation to yield phenols.

The challenges that remain to be uncovered for copper-catalysed reactions are the universal mechanism(s), the role and efficiency of additives (diamines, tertial amines, amino acids, oxidative agents), and further general scope and limitation. The latter is of greater importance for aryl donor amidations.



Scheme 5 Proposed mechanisms for copper-catalysed arylation (Ar = aryl, X = halide, M = metallic reagent (e.g. *B(OH)₂* and *BiAr₂*), R = subtituent, Y = *O*, *NH* or *S*)

1.3 Electrophilic Amination

Electrophilic amination is yet another method for carbon-nitrogen bond formation [32]. The *electrophilic* aminating agents can be divided into two major groups:

(a) the *nitrenoid-like* species, generated from sulfonamide and hydroxylamine derivatives, which are the a^1-synthons delivering $^+NR_2$ equivalents.

(b) *neutral* reagents such as sulfonyl azides [33], oxaziridines [34], diazocarboxylates and unsymmetrical azo compounds, which are stable and isolatable compounds.

The advantage of neutral reagents is that they react under mild/considerably mild reaction conditions and are more chemoselective.

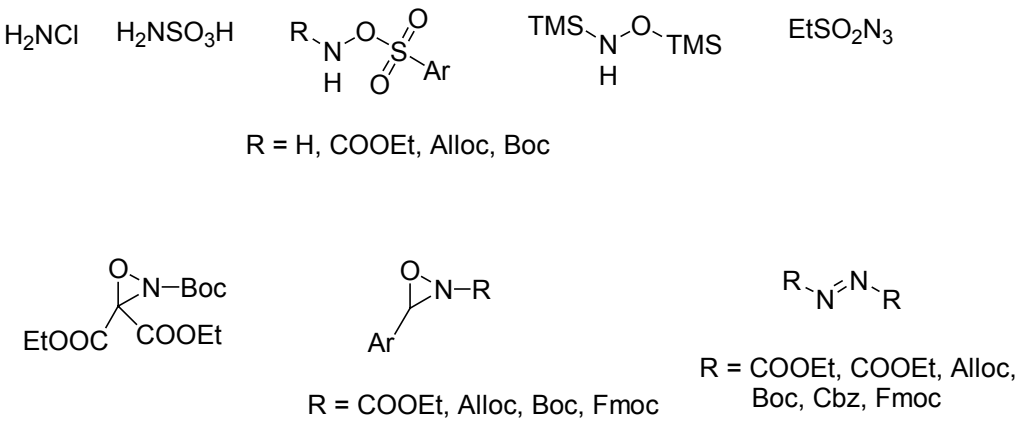


Figure 3 Aminating agents

A number of asymmetric electrophilic amination protocols were developed for the neutral aminating reagents employing their coordination to the metal-ligand complex (e.g. $Cu(OAc)_2$-chiral 1,2-diamine for amination of encarbamates [11]) or the coordination *via* hydrogen bonding in organocatalytic reactions (e.g. proline-catalysed amination of carbonyl compounds [9]).

Despite the growing interest in carbon-nitrogen bond formation, there is only a hand-full of reports on *N*-alkynylation. The known protocols fall into two strategies: *(a)* amine/amide is deprotonated with a strong base generating anion that displaces halide of R-C≡C-Hal [35], and *(b)* copper-catalysed *N*-alkynylation of amides [36] and heterocycles in analogy with Buchwald-Goldberg amidation of aryl halides. Both methods employ harsh reaction conditions and have to be optimised for nearly each substrate. C(alkynyl)-N bond formation seems to have received little attention, but unstable ynamines and stable ynamides are becoming important in heterocyclic chemistry [37]. Another expanding field is "click" methodology,[1] which has a great potential in chemical biology as an bioorthogonal investigation tool for target identification, isolation, visualisation, Cu(I) *in vivo* detection [38], and MRI.

1.4 Organocatalytic Reactions

The term *organocatalysis* was originated by MacMillan and describes the reactions in which small molecules and oligopeptides act as catalysts [39]. Reactions employing metal salts and their complexes do not fall into this category.

The modern organocatalysis dates back to late 1990's-early 2000's when a number of asymmetric reactions were reported to be efficiently catalysed by small molecules. For instance, application of proline **1** and rationally designed imidazolidinone **2** (MacMillan catalyst) in asymmetric aldol condensation [40], Jacobsen thioureas (e.g. **3**) [42] in Strecker and Mannich reactions, and *chincona* alkoloids such as quinine **4** in asymmetric *C*-alkylation under phase-transfer catalysis and in Morita–Baylis–Hillmann reaction [43]. The general interest in small organic molecule not metal-based catalysis was heated by the fact that it allowed to a simpler pathway for stereoselective synthesis.

[1] Copper(I)-catalysed Huisgen 1,3-dipolar addition of azides and terminal alkynes

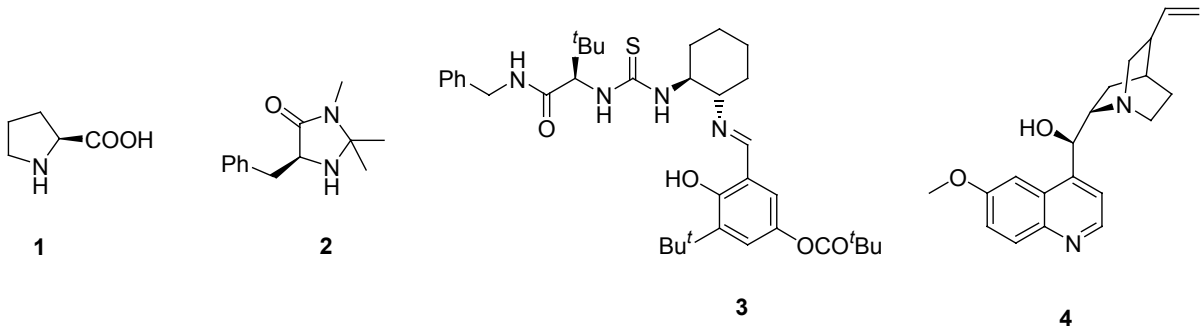
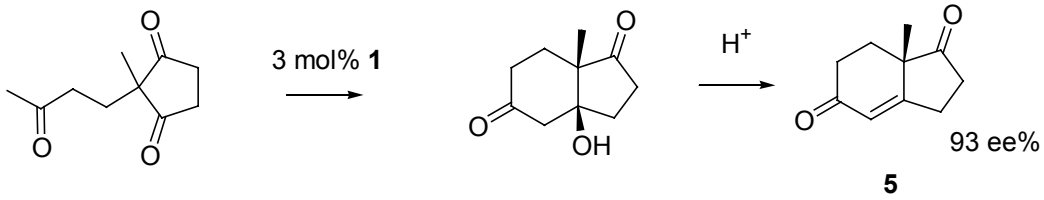


Figure 4 Privileged organocatalysts

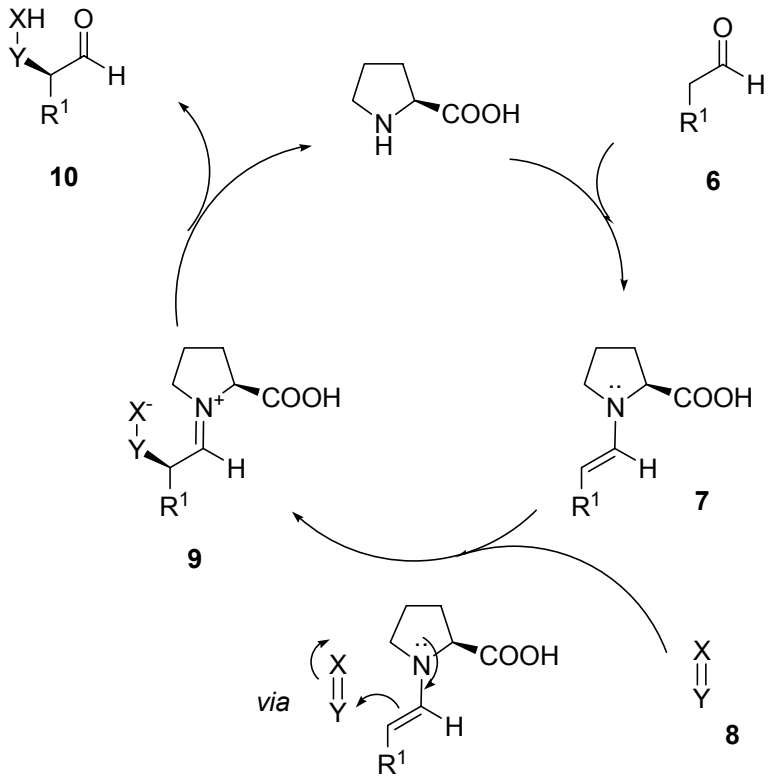
List and Barbas III reported the use of proline as catalyst in asymmetric aldol condensation in 1998 [44]. Their work was prompted by a report in 1970's on Robinson annulation, which afforded **5** in the presence of catalytic amount of proline (Scheme **6**) [45]. The exact catalytic behaviour of amino acid was not understood then. Puchot proposed incorporation of two proline molecules in transition state [46]. His conclusions were based on positive non-linear effect. However, this non-linear effect was later attributed to solid-liquid phase behaviour of proline and other amino acids [47].

After proline was found efficient in aldol condensation, it was applied to other reactions allowing high stereoselectivity (e.g. cross-aldol condensation [48]) as well as led to the development of new reactions (e.g. amination [9, 31e] and aminooxylation/hydroxyamination [49] of carbonyl compounds) including several multicomponent ones [50].



Scheme 6 Stereoselective Robinson annulation

As of today, the mechanistic bases for the proline-induced asymmetric catalysis are well understood [51]. First, proline condensates with enolisible aldehyde **6** (or ketones, although less efficiently) to give enamine **7** (Scheme **7**). Here the concentration of enamine is much higher then that of enone-form in aldehyde solution, thus increasing the both amount electrophilicity and of species that may further attack electrophile **8** to afford **9.** This adduct is then hydrolysed to afford final product **10** and proline, which enters the catalytic cycle once again.

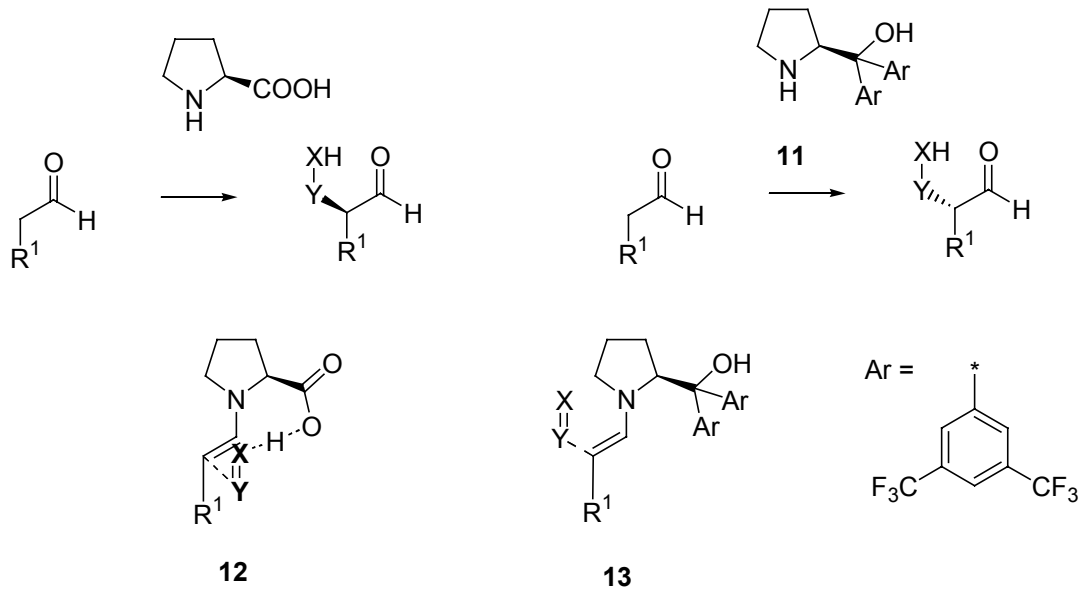


Y=X: C=O, C=N, N=N, N=O/O=N

Scheme 7 Mechanism of proline-catalysed reactions

The stereoselectivity in this proline-catalysed reaction is defined first by the formation of **7** as a major product (*trans*-isomer), and by coordination of electrophile **8** from the plane carboxyl group that also enhances the reaction by local hydrogen bond formation (**12** in Scheme **8**). If carboxyl group in proline is substituted with a bulky moiety such as in Jørgensen catalyst **11** [52], the stereochemical outcome is opposite to that of proline [9]. The bulky group leads to the addition of X=Y from another side of pyrrolidine ring (compare **12** and **13**), while the absence of hydrogen bonding here decreases the reaction rate.

By now, a variety of substrates were investigated in proline-mediated reactions (aldehydes, ketones, azodicarboxylates, nitroso compounds, and activated imines). However, there are no reports of hydrazones acting as electrophiles.



Scheme 8 Transition states for proline and Jørgensen catalyst

Results and Discussion

2.1 Aim

The aim was to complete work on comparative studies on *N*-arylation of carbamate-protected hydrazones, and elaborate on further project that could be of potential use in carbon-nitrogen bond formation.

2.2 Copper-catalysed *N*-arylation of carbamate protected hydrazones[2]

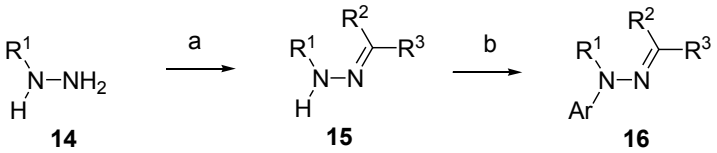
Carbon–nitrogen bond formation remains one of the most extensively reviewed areas in organic chemistry, with palladium [27], nickel [26] and copper-catalysed [25] *N*-arylations playing an important role in the toolbox of organic synthesis. However, some of these methods have drawbacks. Palladium salts are expensive, toxic and require the use of phosphines, *N*-heterocyclic carbenes or other ligands. Nickel catalysts have been reported to show low tolerance to functional groups and to be highly toxic. At the same time, copper-mediated reactions have gained popularity due to mild reaction conditions and the applicability to a variety of aryl donors.

Substituted hydrazines are important in a diverse array of fields, including agrochemicals and pharmaceuticals [1]. Recently, several aspects of copper-catalysed *N*-arylation of hydrazines [53] and azo compounds [10] were studied within our group. In the present study we focused on hydrazones, since they are appealing precursors to monoarylated and 1,1-disubstituted hydrazines as well as to a number of azaheterocycles, inorganic heterocycles and indoles [2]. Previously, to allow the synthesis of such compounds, only palladium catalysis was employed.

The hydrazones of interest were prepared by condensation of hydrazines with the corresponding aldehyde or ketone as previously described (Scheme **10**) [54]. In the presence

[2] The following text was submitted and published in *Tetrahedron Lett.*

of copper(II) diacetate benzophenone hydrazone with a free amino moiety underwent rapid oxidation to afford the symmetric azine $Ph_2C{=}NN{=}CPh_2$ (92%), while the carbamate protected hydrazone derivatives were found to be stable against oxidation. However, carbamate protection increases the amidic nature of the hydrazones, which compared to amines, show poorer reactivity towards arylation.



Scheme 10 Preparation of arylated hydrazones. *Reaction conditions:* (a) ketone/aldehyde, H^+, reflux; (b) arylating agent, $Cu(OAc)_2$, Et_3N.

Entry	Bi reagent	Cu salt	Solvent	Temperature	Time (d)	Yield (%)
1	Ph_3Bi	$Cu(OAc)_2$	DCM	rt	3	92
2	Ph_3Bi	$Cu(OAc)_2$	DCE	reflux	1	97
3	$Ph_3Bi(OAc)_2$	$Cu(OAc)_2$	DCM	rt	3	89
4	Ph_3Bi	$Cu(OAc)_2$	DCM	rt	1	72
5	Ph_3Bi	CuCl	DCM	rt	1	20
6[b]	Ph_3Bi	$Cu(OAc)_2$	MeOH	rt	1	n.r.[c]

[a]Reaction conditions: hydrazone **15a** (0.427 mmol), Bi reagent (1.5 equiv), Cu salt (1.5 equiv), Et_3N (1.5 equiv), solvent (3 mL). [b]Without Et_3N. [c]No product formation was detected by TLC.

Table 1 Optimization of the *N*-arylation of Boc-protected acetophenone hydrazone **15a**[a]

Primarily, optimization of the reaction with triarylbismuthane and its diacetate with Et_3N serving as a promoter showed that the former reagent gave slightly improved results (Table **1**). When the reaction was carried out at ambient temperature in dichloromethane (DCM), the yield of **16aa** approached 70% over 24 h and 90% over three days. When the reaction mixture was heated under reflux in 1,2-dichloroethane (DCE), the starting material **15a** was consumed within 24 h. Copper(II) acetate gave superior results compared to copper(I) chloride, which is in accordance with mechanistic considerations. Previously, *N*-arylation using arylboronic acids as aryl donors carried out in methanol was shown to be successful

even with catalytic loadings of the copper(II) salt [55]. However, when we used organobismuthanes in methanol, no reaction was detected even upon heating under reflux.

In general, *N*-arylation of carbamate-protected hydrazones takes place under mild reaction conditions (Table **2**), and can be employed as a convenient alternative to Buchwald–Goldberg amidation [28]. The yield of the phenylated product of Boc-protected benzaldehyde hydrazone, **16ca**, was 44% due to partial decomposition during purification on silica gel. Arylation of the aminic nitrogen in 2-phenyl benzophenone hydrazone **15d** with *p*-Tol_3Bi proceeded in 24 h to afford the corresponding product **16db** in 98% isolated yield.

Entry	R^1	R^2	R^3	Ar	**15**	**16**	Conditions	Time (d)	Yield (%)
1	Boc	Ph	Me	Ph	**15a**	**16aa**	A	1	97
2	Boc	Ph	Me	*p*-Tol	**15a**	**16ab**	B	3	90
3	Boc	Ph	Me	*o*-Tol	**15a**	**16ac**	B	3	10
4	Boc	Ph	Me	*p*-An	**15a**	**16ad**	B	3	96
5	Boc	CH=CHPh	Me	Ph	**15b**	**16ba**	B	3	72
6	Boc	Ph	H	Ph	**15c**	**16ca**	A	1	44[b]
7	Ph	Ph	Ph	*p*-Tol	**15d**	**3db**	A	1	98

[a]Reaction conditions: hydrazone (1 equiv), Ar_3Bi (1.5 equiv), $Cu(OAc)_2$ (1.5 equiv), Et_3N (1.5 equiv); conditions A: DCE, heating under reflux; conditions B: DCM, rt.[b]Partially decomposed on the silica column.

Table 2 Copper(II) acetate-catalysed *N*-arylation of hydrazones **15** with triarylbismuthanes[a]

The only limitation is in the introduction of sterically hindered aryls. The reaction of **15a** with *o*-Tol_3Bi over three days gave only a 10% yield. Arylation with both 1-Np_3Bi and 1-$Np_3Bi(OAc)_2$ yielded no product. Raising the temperature and using different promoters (*t*-BuOK, Py, Et_3N, DBU, DMAP) did not lead to an increase in reactivity and only the formation of 1-NpOAc was detected by TLC. Thus, it as has been previously reported, introduction of sterically congested aryl substituents with bismuth reagents is somewhat complicated [29, 30].

As a comparison, arylation with arylboronic acids [29], which are less sterically hindered and more "aryl-economic", was attempted. Reaction of hydrazone **15a** with $PhB(OH)_2$ in DCM over three days yielded 4% and 7% of the product in the presence of Et_3N and pyridine,

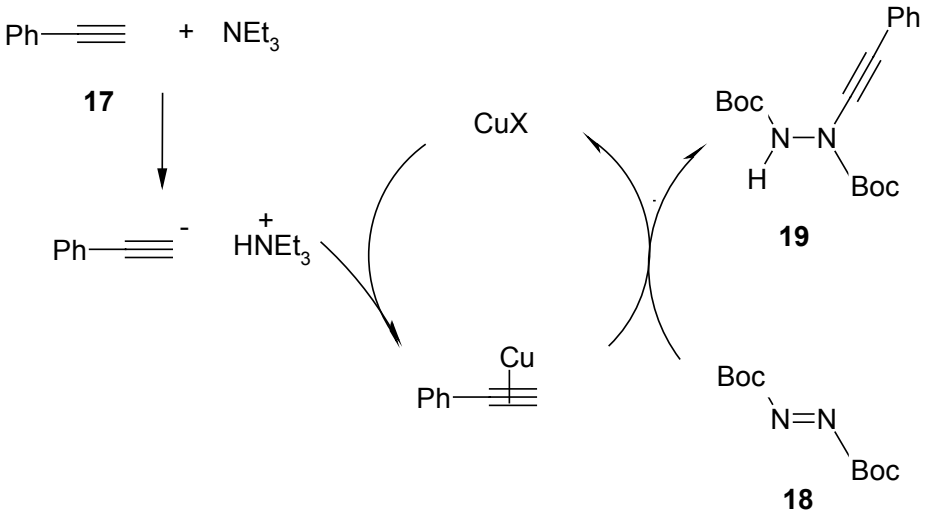
respectively. No reaction was detected with 1-NpB(OH)$_2$. Reaction of **15a** with PhB(OH)$_2$ in methanol with heating under reflux for three days afforded only 15% of the product.

In summary, we have demonstrated the applicability of organobismuth reagents rather than arylboronic acids in the copper-catalysed *N*-arylation of amidic nitrogen. The carbamate protected hydrazones used as model substrates generally give good to excellent yields under mild reaction conditions. Taken together, this method represents a useful alternative to Buchwald–Goldberg amidation and can be successfully applied to the synthesis of trisubstituted amides and hydrazides.

2.3 Towards Electrophilic Amination of Terminal Acetylenes

Electrophilic amination of a number of substrates including aldehydes, ketones [9], alkenes [56], nitroolefines [57], alkylidene cyanoacetates and malononitriles [58] was reported with dialkyl azodicarboxylates. A remarkable amination of arylboronic acids and organobismuthanes was achieved with less activated unsymmetrical azo compounds [10].

Terminal alkynes are well-known nucleophiles and we suggested that they would easily react "atom-economically" with azo compounds (Scheme **11**). In general, alkynes have to be activated and there are several methods to achieve it. Strong bases such as BuLi and ^{i}PrMgCl deprotonate alkyne and copper and zinc salts lead to acetylides *in situ* [59]. The copper-based method is the mildest and only catalytic amounts of salt are usually needed.



Scheme 11 Proposed mechanism of electrophilic amination of terminal acetylenes

At first, we examined reaction between phenylacetylene **17** and di-*tert*-butyl azodicarboxylate **18** with equimolar amount of copper(II) acetate and triethylamine as tertial amine base. The starting material **18** was consumed in less than ten minutes under heating in MeOH with formation of one UV-active compound and BocNHNHBoc as the only by-product. However, ^{1}H NMR, ^{13}C NMR, and IR spectra (see Appendix) showed that it was not the desired product **19**. Two additional amide hydrogens are seen in ^{1}H NMR and IR, while NMR and IR spectra show the presence of both Boc and phenylacetylenide. UV-MS showed a single sharp peak in UV, but the adduct decomposed in MS. The MALDI-MS spectrum (Figure **5**) distinctively showed that we were dealing with a hexamer. It is impossible to draw conclusions on structure of the unknown compound solely based on aforementioned data. The same compound was afford in 30-80 mg range when the reaction was carried out with various copper courses (CuI, CuCl, CuBr, $Cu(OTf)_2$) in a number of solvents (MeOH, EtOH, THF, MeCN, DCM). In toluene with CuCl as catalyst (at rt) corresponding 1,4-diphenylbutadiyne was afforded as sole product in quantative yield.

No reaction was detected with less activated azo compound PhN=NBoc under different conditions ($Zn(OTf)_2$/TEA/DMAE and Cu(I or II)/TEA/Δ). With PhC≡CLi a complx mixture of compounds was formed.

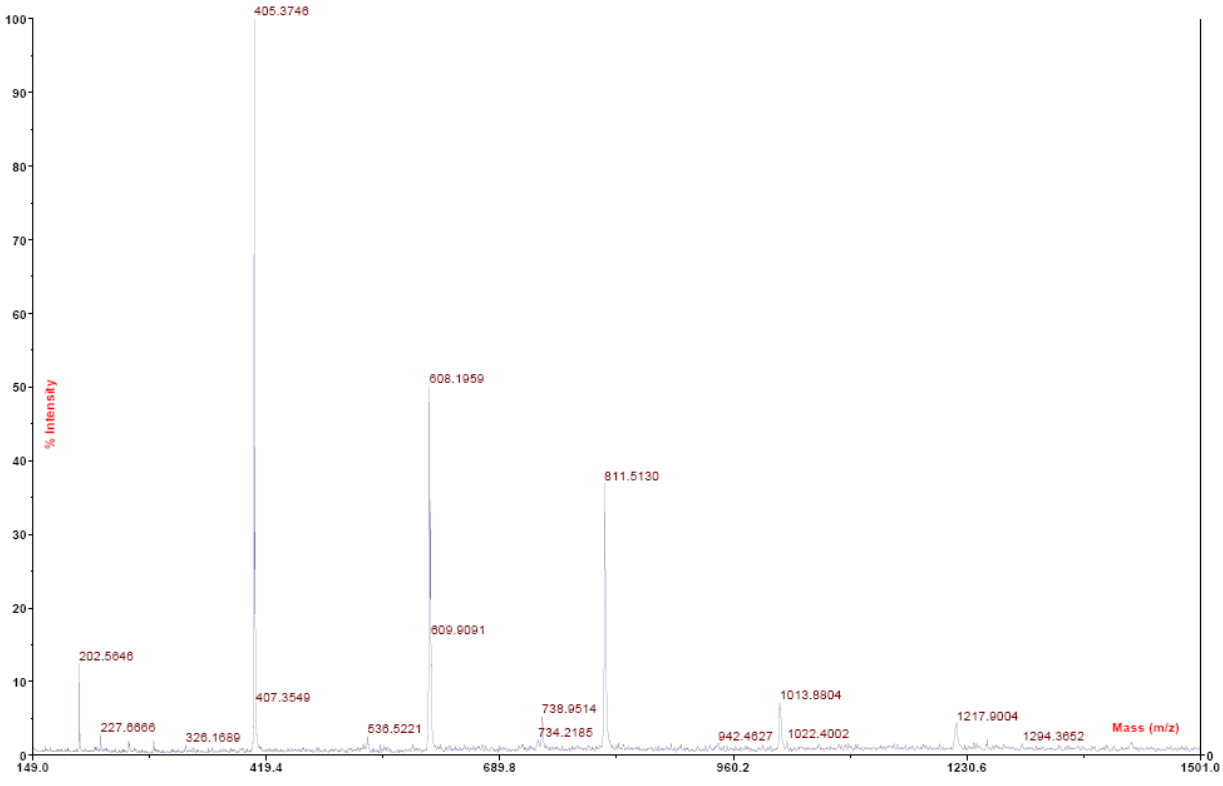


Figure 5 MALDI-MS spectrum of unknown compound

Based on these experiments, we conclude that electrophilic amination of terminal acetylenes by azo compounds and dialkyl azocarboxylates, in particular, is possible. However, the intermediate may further react with starting material to give oligomeric compounds. Thus, further optimisation of reaction conditions is needed together with better understanding of the factors involved in the process of oligomerisation.

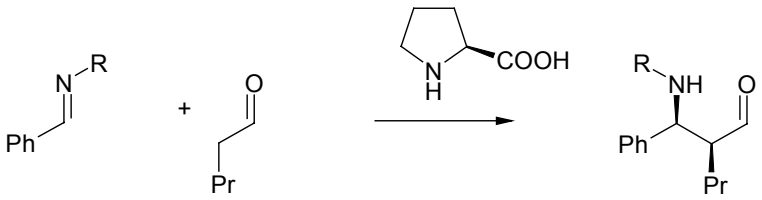
2.4 Towards Organocatalytic Synthesis of *β*-Hydrazino Carbonyl Compounds

β-Amino carbonyl compounds represent an important class of building blocks for various synthetic targets [60]. Although a number of asymmetric Mannich [61] and aza-Morita-Baylis-Hillmann [62] approaches including organocatalysis and chiral metal complex-catalysed reactions were described, there are no direct and/or multicompotent organocatalytic examples involving hydrazones as C=N electrophiles.

Proline-catalysed Mannich reaction was previously carried out directly or with preformed *N*-anisylaldimines [61b]. Furthermore, substitution of anisyl with *tert*-butyloxycarbonyl moiety resulted in remarkably improved *syn*/*anti* ratio and diastereoisomeric excess (both reaching over 99:1 with yields of 73-91%), and only the reaction with alkylaldehyde-derived imine (BocN=CH-c-Hex) had failed (less then 5% yield) [63]. An increase in stereoselectivities was attributed to enrichment by precipitation (the product crystallised out of reaction), while enhanced reaction rate to higher electronegativity of Boc compared to anisyl.

Inspired by aforementioned results we aimed to testing analogical conditions employing a different type of azomethine substrates – hydrazones, which are more stable than imines. However, all our attempts had failed and further we discuss details of suggested experiments (summarised in Table **1**) and explain the background.

The main obstacle we encountered was the poor electrophilicity of hydrazones to that of imines. Imines are less polarised then aldehydes and thus show poor or no reactivity. This is due to lower electronegativity of nitrogen than that of oxygen. Although in some Mannich reactions additional enantio- and/or diastereomeric amplification and reaction acceleration can be caused by *autocatalysis* [64], it is not appropriate in our case. The *autoinduction* phenomena observed for analogical proline-catalysed α-amination and α-aminooxylation, cannot be applied for Mannich reactions either [64]. Additionally, imines are not stable and may easily undergo hydrolysis.



20a: R = NHBoc; **20b**: R = $NBoc_2$; **20c**: R = NHTos

Entry	Hydrazone	organocatalyst, amount	additive	conditions	Observations by TLC
1	**20a**	*(S)*-proline, 20 mol%	–	MeCN, 0 °C	after 12 h starting material not consumed
2	**20b**	*(S)*-proline, 10 mol%	–	MeCN, rt	after 13 h starting material not consumed
3	**20b**	*(S)*-5-pyrrolidin-2-yltetrazole, 10 mol%	–	DCM, rt	after 11 h starting material not consumed
4	**20c**	*(S)*-proline, 20 mol%	–	MeCN, rt	after 13 h starting material not consumed
5	**20a**	*(S)*-proline, 10 mol%	$Mg(ClO_4)_2$, 5 mol%	DCM, rt	after 12 h starting material not consumed, benzaldehyde detected
6	**20c**	*(S)*-proline, 10 mol%	$Zn(OTf)_2$, 20 mol%	DCM, rt	after 14 h starting material not consumed, benzaldehyde detected
7	**20c**	*(S)*-proline, 10 mol%	$Cu(OTf)_2$, 20 mol%	DCM, rt	after 14 h starting material not consumed, benzaldehyde detected
8	**20c**	*(S)*-proline, 20 mol%	1.1 equiv TMSCl, 2.1 equiv MeOH	DCM, rt	after 4 h starting material not consumed, benzaldehyde detected
9	**20c**	*(S)*-proline, 20 mol%	1 equiv conc HCl	DCM, rt	after 2 h starting material not consumed, benzaldehyde detected
10	**20c**	*(S)*-proline, 20 mol%	2 equiv thiourea	DCM, rt	after 17 h starting material not consumed
11	**20c**	*(S)*-proline, 20 mol%	5 equiv I_2	MeCN, rt	after 19 h starting material not consumed, benzaldehyde detected

Table 1 Attempted Mannich reaction with hydrazones **20**

However, several strategies to enhance the reactivity of imines have been reported. This is usually achieved by using electronegative protecting groups such as *N*-An, *N*-Boc, *N*-Tos or using imines derived from ethyl glyoxylate or aryl or fluorinated aldehyde. However, the use of electronegative group such as Boc and Tos on adjacent to azomethine nitrogen did not raise the reactivity (entries 1–4 in Table **1**).

Another method to activate imines employs activation by Lewis acids (activation *via* bidentate complexation). However, affinity of resulting amines to these species is high leading to decreased overall efficiency. We have used $Mg(ClO_4)_2$, $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, $Zn(OTf)_2$ but no reaction except partial hydrolysis of C=N bond was detected. The latter may be attributed to the minimal water content from enamine formation in the first step of organocatalysis. Addition of concentrated HCl (36.5% HCl), and anhydrous HCl generated *in situ* from TMSCl and MeOH [65] to give rise to iminium chloride led nowhere but to hydrolysis. Pretreating of BocNHN=CHPh with benzyl chloroformate did not afford the desired product formation.

Another activator/co-organocatalyst that we have tried was thiourea. It was shown to activate imines in direct aminative reduction of ketones with Hantzsch ester [66] by preferential *double* hydrogen bonding to imines [67, 42e]. However, in our case only the starting material was observed.

Molecular iodine is a mild Lewis acid and activates *N*-arylimines towards nucleophilic addition with silyl enol ethers and TMSCN and hydrolysis via iodonium ion [68]. When we used iodine with **20c** only hydrolysis of *N*-tosylhydrazone was detected. At the same time no reaction was detected when **20b** and I_2 (5 equiv) were mixed in $MeCN/H_2O$ (9:1).

In summary, despite the intensive research in C=N bond activation, its reactivity highly depends on substituents in imine and general reaction conditions. We showed that activation of hydrazones to the attack by enamine is impossible under standard mild systems. Firstly, α-effect[3] [69] is contributing to greater inactivation of hydrazones than that of imines. Secondly, since charge distribution (AM1) and exhibited reactivity in a series of imines and hydrazones do not correlate, we believe that the hydrogen bonding, and to some extent sterics, play crucial role in organocatalytic Mannich reaction.

[3] "The enhanced reactivity of nucleophiles that have an unshared pair of electrons on the atom adjacent to the nucleophilic centre, relative to a normal nucleophile of the same basicity" [69b]

Experimental Section

3.1 General

Monitoring of reactions was performed using silica gel TLC plates Merck 60 F254. Spots were visualized by UV light at 254 nm or by alcoholic solution of phosphomolybdic acid with subsequent heating. Column chromatography was carried out on Merck Kieselgel 70-230 mesh. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. The chemical shifts are reported in ppm (9 scale) using TMS as reference. Melting points were measured on a Gallenkamp melting point apparatus. IR absorption spectra of oils were recorded as a thin film, and of solid compounds as a nujol mull, both on KBr plates and the values are reported in cm^{-1}. Positive ion mass spectra were recorded on an Ettan ESI-ToF electrospray time-of-flight mass spectrometer (Amersham Biosciences, Uppsala, Sweden) at capillary exit voltages 80–150 V and capillary temperature 170 °C. Electrospray tuning mix (Agilent, USA) was used for calibration of the instrument. Samples were dissolved in HPLC grade acetonitrile or methanol (Sigma-Aldrich, Germany) and infused at 10–50 μL/min via ESI source using a syringe pump. General procedure for preparation of hydrazones is described elsewhere [54, 70]. Organobismuthanes [71] and arylboronic acids [72] were prepared as previously described. Valeraldehyde and phenylacetylene were purified according to known protocols [73]. Copper(II) acetate was dried at 90 °C *in vacuo* (1 mm Hg). All remaining reagents were used as supplied without prior purification.

3.2 Copper-Catalysed *N*-Arylation

N-Arylation with organobismuthanes: Hydrazone (0.427 mmol; 1 equiv) was dissolved in DCM or DCE (3 mL), then TEA (1.5 equiv), $Cu(OAc)_2$ (1.5 equiv equiv), Ar_3Bi (1.5 equiv)

were added and left to stir at rt (in DCM) or at 50 ºC (in DCE). The reaction was monitored by TLC, using EtOAc/hexanes 1:5 as eluent. The product was isolated by column chromatography. Firstly, EtOAc/hexanes 1:30 was used to elute most of unpolar components. Then, elution was continued using EtOAc/hexanes 1:5. The fractions containing the arylated hydrazone were combined and solvent was evaporated *in vacuo*.

N-Arylation with arylboronic acids: Hydrazone (0.427 mmol; 1 equiv) was dissolved in solvent (3 mL), then promoter (1.5 equiv), $Cu(OAc)_2$ (1.5 equiv) and $PhB(OH)_2$ (1.5 equiv) were added. The reaction was monitored by TLC, using EtOAc/hexanes 1:4 as eluent. The product was isolated by column chromatography, using EtOAc/hexanes 1:4 as eluent. The fractions containing the arylated hydrazone were combined and solvent was evaporated *in vacuo*.

tert-Butyl 1-phenyl-2-(1-phenylethylidene)hydrazinecarboxylate: IR (film, KBr) *v* 3396, 2975, 1710, 1589, 1494, 1373, 1298, 1153 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) *δ* 8.00–7.00 (m, 10H), 2.27 (s, 3H), 1.49 (s, 9H), ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 172.1, 151.6, 142.7, 137.7, 130.5, 128.5, 128.4, 127.2, 125.2, 124.2, 81.9, 28.4, 17.1; HRESIMS *m/z* 333.1587 $[M+Na]^+$, calcd for $C_{19}H_{22}N_2NaO_2$ 333.1579.

tert-Butyl 2-(4-phenylbut-3-en-2-ylidene)hydrazinecarboxylate: Yield 84%. Pale yellow crystals. For the assignment of mp the product was recrystallized from EtOH. Mp 156.1–156.4 °C. IR (KBr, pellet) N 3182, 2978, 2360, 1724, 1696, 1534, 1244, 1146, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (br s, 1H). 7.5–7.2 (m, 6H), 6.94 (dd, 1H, J = 16.2, J = 31.2) 2.00 (s, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.5, 148.4, 136.4, 132.4, 129.3, 128.6, 128.1, 126.7, 81.3, 28.2, 10.5; HRESIMS m/z 283.1470 $[M+Na]^+$, calcd for $C_{15}H_{20}N_2O_2Na$ 283.1423.

tert-Butyl 1-(4-methylphenyl)-2-(1-phenylethylidene)hydrazinecarboxylate: Yellow viscous oil. IR (KBr, film) N 3371, 2974, 2924, 2367, 2337, 1704, 1504, 1368, 1328, 1288, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.0 (m, 9H), 2.32 (s, 3H), 2.27 (2, 3H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.7, 151.8, 140.3, 137.8, 135.0, 130.4, 129.1, 128.3, 127.2, 124.3, 121.2, 81.3, 28.4, 20.9, 17.1; HRESIMS m/z 347.1793 $[M+Na]^+$, calcd for $C_{20}H_{24}N_2O_2Na$ 347.1736.

tert-Butyl 1-(2-methylphenyl)-2-(1-phenylethylidene)hydrazinecarboxylate: Yellow viscous oil. IR (KBr, film) N 3341, 2980, 2924, 2854, 2369, 2342, 1707, 1494, 1459, 1366, 1296, 1253, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.1 (m, 9H), 2.37 (s, 3H), 2.31 (2, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.6, 152.3, 138.1, 135.9, 131.3, 130.8, 130.1, 128.2, 127.7,

127.2, 127.1, 126.5, 81.1, 28.3, 18.3, 17.4; HRESIMS m/z 347.1767 $[M+Na]^+$, calcd for $C_{20}H_{24}N_2O_2Na$ 347.1736.

tert-Butyl 1-(4-methoxyphenyl)-2-(1-phenylethylidene)hydrazinecarboxylate: Yellow viscous oil. IR (KBr, film) N 3301, 2970, 1695, 1514, 1369, 1298, 1243, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–6.8 (m, 9H), 3.78 (s, 3H), 2.29 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.3, 157.5, 152.0, 137.8, 136.0, 130.4, 128.3, 127.2, 126.3, 122.3, 113.9, 81.2, 55.5, 28.4, 17.1; HRESIMS m/z 363.1696 $[M+Na]^+$, calcd for $C_{20}H_{24}N_2O_3Na$ 363.1685.

tert-Butyl 1-phenyl-2-(4-phenylbut-3-en-2-ylidene)hydrazinecarboxylate: Yellow viscous oil. IR (KBr, film) N 3441, 2985, 1735, 1493, 1318, 1258, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.0 (m, 12H), 2.08 (s, 3H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.1, 152.3, 143.2, 137.9, 136.3, 129.6, 129.3, 129.0, 127.8, 126.0, 125.1, 81.3, 28.2, 15.5; HRESIMS m/z 359.1677 $[M+Na]^+$, calcd for $C_{21}H_{24}N_2O_2Na$ 359.1736.

tert-Butyl 1-phenyl-2-benzylidenehydrazinecarboxylate: Yellow viscous oil. IR (KBr, film) N 3296, 2980, 1704, 1589, 1494, 1368, 1338, 1253, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0 (br s, 1H), 7.7–7.0 (m, 10H), 1.491 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.1, 142.8, 137.6, 134.9, 130.1, 129.8, 129.4, 129.0, 127.5, 82.1, 28.5; HRESIMS m/z 319.1406 $[M+Na]^+$, calcd for $C_{18}H_{20}N_2O_2Na$ 319.1423.

2-(Diphenylmethylene)-1-phenyl-1-p-tolylhydrazine: Yellow viscous oil. IR (KBr, film) N 3059, 3023, 2921, 1590, 1487, 1266, 1210, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8–6.8 (m, 19H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 149.3, 145.9, 139.4, 137.8, 133.6, 130.0, 129.9, 129.0, 128.6, 128.5, 128.3, 128.2, 21.3; HRESIMS m/z 363.1868 $[M+H]^+$, calcd for $C_{26}H_{23}N_2$ 363.1861.

3.3 Electrophilic Amination

tert-Butyl diazocarboxylate: *tert*-Butyl carbazate (1.451 g, 10.97 mmol) and di-tert-butyl dicarbonate (2.396 g, 10.97 mmol) were mixed for 4 h at rt in DCM (10 mL). The solvent and ^{t}BuOH were evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and pyridine (0.955 g, 12.07 mmol), and NBS (2.150 g, 12.07 mmol) was added at 0 °C. The reaction mixture was stirred at rt until BocNHNHBoc was consumed (0.5 h), then the solvent was evaporated under reduced pressure and DBAD was purified by recrystallisation (2.122 g, overall 84%) from hexane (5 mL).

Copper-calysed protocol: Phenylacetylene (47 μL, 0.434 mmol) was added to the mixture of copper(II) acetate (79 mg, 1.0 equiv) and TEA (61 μL, 1.0 equiv) in methanol (2 mL). Then, DBAD (100 mg, 0.434 mmol) was added and the mixture was refluxed at 65 °C (water bath). After starting material was consumed, solvent was evaporated under reduced pressure and residue was purified by column chromatography (EtOAc/hexane 1:4) to yield colourless crystals (80 mg) of unknown compound, mp (hexane): 114.5-114.7 °C. ^{1}H NMR, ^{13}C NMR, IR, UV-MS, and MALDI-MS spectra are attached (see Appendix).

Zinc triflate-catalysed protocol [74]: A flask was charged with $Zn(OTf)_2$ (79 mg, 0.50 equiv) and heated for 3 min. The flask was cooled to rt and flushed with argon. Then, DCM (1.5 mL), TEA (61 μL, 1.0 equiv), and DMAE (44 μL, 0.5 equiv) were added. The resulting mixture was stirred at rt for 1.5 h before the phenylacetylene (47 μL, 1.0 equiv) was added, followed by PhN=NBoc (90 mg, 0.436 mmol) solution in DCM (0.5 mL) in 0.5 h. After 17 h, starting material was not consumed and no UV-active product was formed.

3.4 Mannich Reaction

di-tert-Butyl 2-benzylidenehydrazine-1,1-dicarboxylate: To a solution of BocNHN=CHPh (**20a**; 1.375 g, 6.24 mmol) in MeCN (5 mL) were added DMAP (76 mg, 0.624 mmol) and di-*tert*-butyl dicarbonate (1.362 g, 6.24 mmol) and the mixture was left to stir overnight (14 h). Solvent was then evaporated and the residue was purified by chromatography on a short silica column (EtOAc/hexane 1:4) to afford colourless crystals (1.772 g, 89%), mp (hexane) 71.8-72.0 °C.^{1}H NMR δ ($CDCl_3$) 1.55 (18H, s), 7.41 (3H, m), 7.75 (2H, m), 8.28 (1H, s). ^{13}C NMR δ ($CDCl_3$) 28.0, 83.6, 128.0, 128.6, 130.9, 133.8, 150.7, 156.8. IR (KBr, pellet) 3448, 2986, 2970, 1744, 1734, 1616, 1366, 1274, 1107 cm^{-1}.

*General procedure (entry 1 in Table **1**):* To a clear solution of hydrazone **20a** (50 mg) in MeCN (4.5 mL) were added *(S)*-proline (5 mg, 20 mol%) and valeraldehyde (120 μL, 5 equiv), and the mixture was left to stir at 0 °C. After 12 h, starting material (hydrazone) was not consumed.

Further reactions were attempted on 50–100 mg scale (**20**) with 5 equiv valeraldehyde and were monitored by TLC (EtOAc/hexane 1:4 for **20a**–**b**; EtOAc/hexane 1:2 for **20c**). For additives and conditions, see Table **1**.

Summary

The extensive research in carbon-nitrogen bond formation is the *raison d'être* for the present study of application of known and development of new mild synthetic methodologies for hydrazine derivatisation.

Firstly, we have demonstrated the applicability of organobismuth reagents rather than arylboronic acids in the copper-catalysed *N*-arylation of amidic nitrogen. The carbamate protected hydrazones used as model substrates generally give good to excellent yields under mild reaction conditions. This method represents a useful alternative to Buchwald–Goldberg amidation and can be successfully applied to the synthesis of trisubstituted amides and hydrazides.

Secondly, we have shown that copper-catalysed electrophilic amination of terminal acetylenes by azo compounds and dialkyl azodicarboxylates, in particular, is possible. However, the intermediate may further react with starting material to give oligomeric compounds. Thus, further optimisation of reaction conditions is needed along with better understanding of factors behind oligomerisation.

Thirdly, we have shown that activation of hydrazones to the attack by enamine is not possible with standard mild systems. Since charge distribution and exhibited reactivity in a series of imines and hydrazones do not correlate, we believe that the hydrogen bonding, α-effect and to some extent sterics, play crucial role in hypothetical organocatalytic Mannich reaction with hydrazones as azomethine equivalents.

Kokkuvõte

Laiaulatuslikud uuringud süsinik–lämmastik sideme moodustamise alal on põhjuseks varemtuntud meetodite rakendamise ja uute meetodite edasiarendamise uurimiseks. Antud magistritöö raames tehti seda hüdrasiini derivaatide näitel.

Esiteks leiti karbamaatkaitstud hüdrasoonide näitel, et vaskkatalüüsitud amiidide arüülimine organobismutaanidega on efektsiivsem kui arüülboroonhapetega. Antud meetod on hea alternatiiv Buchwald–Goldberg'i arüülimisele ning seda saab edukalt rakendada diasendatud amiidide ja hüdrasiidide sünteesil.

Teisalt näidati, et vaskkatalüüsitud terminaalsete alküünide elektrofiilne amiinimine leiab aset asoühenditega ja nimelt dialküül asodikarboksülaatidega. Samas on intermediaat võimeline lähteainega edasi reageerima, andes oligomeerse ühendi. Seega on vaja selle reaktsiooni tingimuste edasist optimeerimist koos parema arusaamisega sellest, kuidas tekib oligomerisatsiooni produkt.

Kolmandaks näidati, et organokatalüütilistes reaktsioonides on hüdrasoonide aktiveerimine raskendatud ja standartsetes pehmetes tingimustes ei ole see võimalik. Kuna arvutatud laengujaotus ning eksperimendi käigus näidatud reaktiivsus imiinide ja hüdrasoonide seerias ei ole omavahel korreleeritavad, jõuti järeldusele, et hüpoteetilises organokatalüütilises Mannichi reaktsioonis hüdrasoonidega kui asometiini ekvivalentidega on suur roll vesinik sidemetel, α-efektil ning mõningal määral ka steerikal.

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Appendix

1. Starkov, P.; Zemskov, I.; Sillard, R.; Tšubrik, O.; Mäeorg, U. Copper-catalyzed *N*-arylation of carbamate protected hydrazones. *Tetrahedron Lett.* **2007,** *48,* 1155–1157.

2. ^{1}H NMR, ^{13}C NMR, IR, UV-MS, and MALDI-MS spectra of the unknown compound (Chapter **2.3**).

3. ^{1}H NMR, ^{13}C NMR, and IR spectra of $Boc_2NN{=}CHPh$ (**20b**).