UNIVERSITY OF PARDUBICE
FACULTY OF CHEMICAL TECHNOLOGY
INSTITUTE OF ORGANIC CHEMISTRY AND TECHNOLOGY

Synthesis of selected nitrogen-containing heterocycles from enamines *via* an intramolecular C–N cross-coupling

DOCTORAL THESIS
(ANNOTATION)

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CONTENT

Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
Bu	butyl
CC	cross-coupling
COSY	Correlation Spectroscopy
dba	dibenzylideneacetone
DCM	dichloromethane
DESA	*N*,*N*-diethylsalicylamide
DMEDA	1,2-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
Et	ethyl
FGA	functional group addition
FGI	functional group interconversion
Het	heteroaryl
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High-Resolution Mass Spectrometry
L	ligand
M	metal
MALDI	Matrix-Assisted Laser Desorption/Ionization
Me	methyl
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
Ph	phenyl
Pr	propyl
Tf	triflate

1 Introduction

CC Reactions belong among the most crucial transformations used in modern synthetic chemistry and are the essential methodologies in the toolbox of every synthetic chemist.[1–5] Protocols allowing successful *N*-arylation of practically all imaginable substrates can be found in the literature.[6–8] The key factor in the widespread adoption of these procedures has been the continuing development of reliable and versatile catalysts that function under operationally simple, user-friendly conditions.[8]

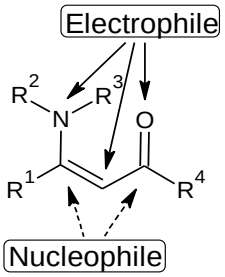


Figure 1 Reactivity of enaminones towards electrophilic and nucleophilic reagents

This doctoral thesis has been focused especially on palladium, but also copper-catalyzed intramolecular C–N CC reaction of easily obtainable acyclic enaminones. These molecules are so called *push-pull* polarized ethylenes which means that both electron-donating and electron-withdrawing groups are included in their structure. As a result, enaminones are capable of reacting with a wide variety of both electrophilic and nucleophilic reagents (Figure 1).[9] On the other hand, the nucleophilicity of the nitrogen atom is lowered (they can be classified as vinylogous amides) in comparison with ordinary amines which makes them relatively challenging substrates for C–N CC. Compared to other substrates, enaminones and related compounds are still rather neglected substrates from this point of view.[10–22]

N-Arylation is influenced by many factors; structure of the starting substrate/s, the choice of an appropriate transition metal, a ligand, a base and a solvent. General formula for successful reaction conditions is not available so the optimization studies are necessary to be carried out in almost all the cases depending on the particular type of substrate. Many different types of catalytic systems were applied on the cyclization of the prepared acyclic enaminones in this work; from the traditional ones to the new palladium precatalysts. Evaluation of their suitability in CC of the corresponding enaminones bearing halide on aromatic or heteroaromatic part of the molecule is discussed and results are given in the next chapter (Results and discussion).

1.1 Objectives

The first target of this doctoral thesis was preparation of tetrahydroquinolines **37b,d, 39b,d, 41a,b** as the direct precursors of some alkaloids from *Galipea Officinalis* (Figure 2).

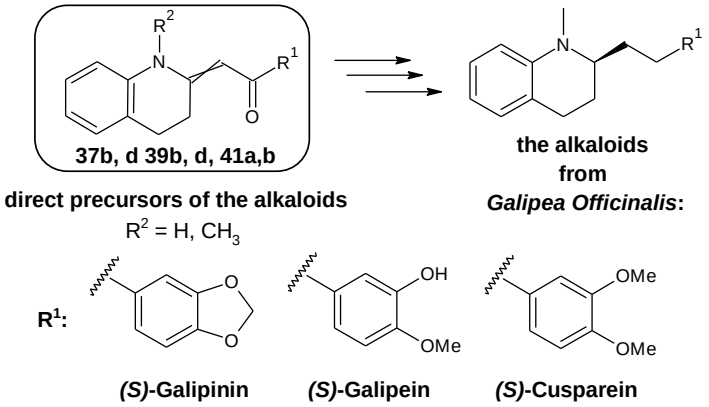


Figure 2 The synthetic approach to the alkaloids

Our approach leading to these moieties (**37b,d, 39b,d, 41a,b**) was based on the intramolecular Buchwald-Hartwig C–N CC reaction of acyclic enaminones **33, 35** (Ar = Ph; R^2 = H, CH_3; X = Br, Cl) bearing bromide or chloride as the leaving group (Figure 3). In the next stage of our research, the methodology was extended to other structurally diverse substrates **33, 35** summarized in Figure 3. The optimal reaction conditions were investigated for the cyclization of aryl/heteroaryl bromides, chlorides and iodides **33, 35** containing both primary and secondary aminogroup. A series of polysubstituted tetrahydropyridines **37–39** was prepared. The scope and limitations of C–N CC reaction of acyclic enaminones were determined.

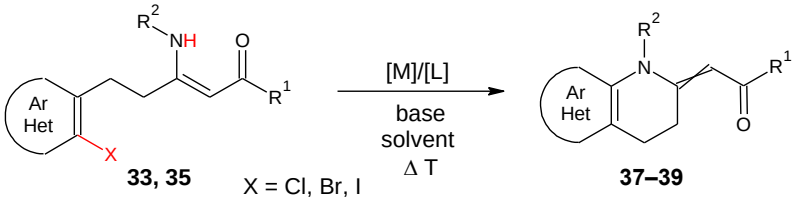


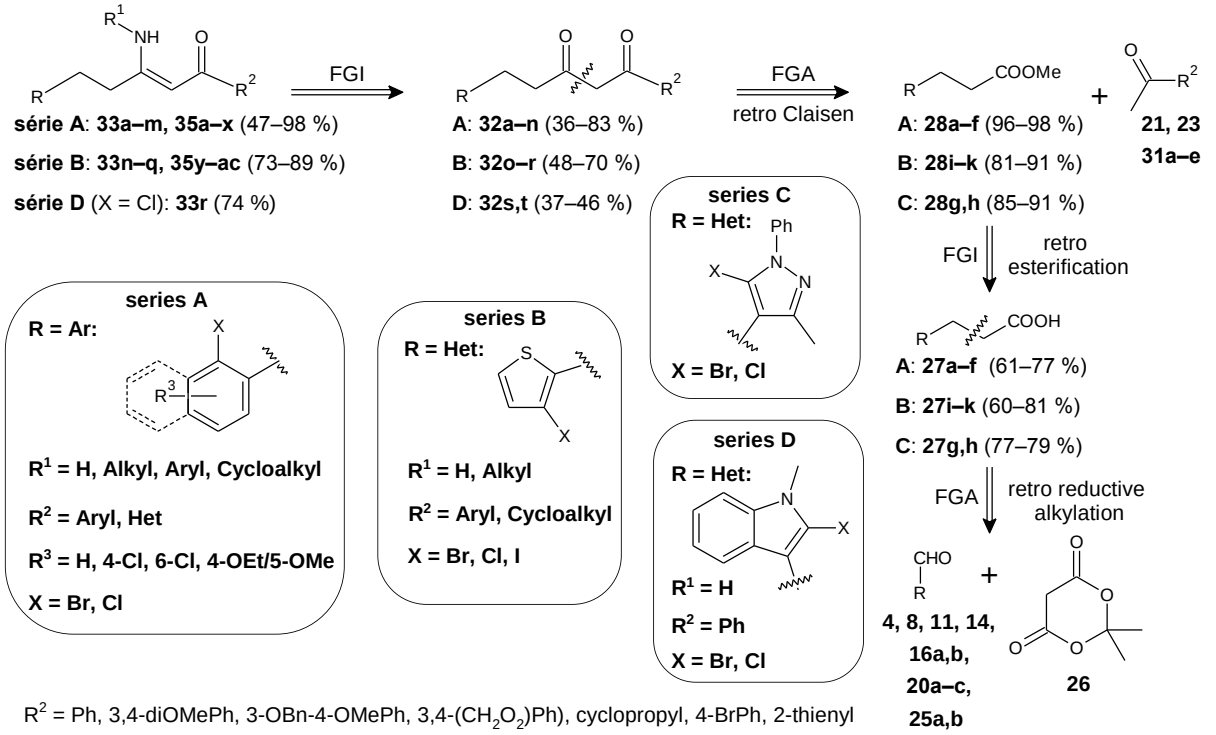
Figure 3 The principal aim of the work

Moreover, screening of a large portfolio of catalysts was developed including new trends in CC (evaluation of suitability for prepared acyclic enaminones **33, 35**). All products and intermediates were characterized and side products were identified.

2 Results and Discussion

2.1 Synthesis of the starting enaminones 33, 35

The simple retrosynthesis of the starting enaminones **33a–r, 35a–ac** lead to the corresponding β-diketones **32a–t** accessible via *t*-butoxide or *t*-pentoxide mediated Claisen condensation of 3-aryl or 3-heteroarylpropionic esters **28a–k** with selected ketones; acetophenone **31a** or its derivatives **21, 23, 31a,b,d**, 2-acetylthiophene **31e** or cyclopropyl methyl ketone **31c** (Scheme 1). Particular esters **28a–k** were synthesized by esterification of the corresponding acids **27a–k** using $SOCl_2$ in MeOH. The best and the least time-consuming route leading to acid **27** consists in the reductive alkylation of Meldrum´s acid **26** by the appropriate aldehyde **4, 8, 11, 14, 16a,b, 20a–c, 25a** in presence of HCOOH/TEA (**24**) system. Aldehydes were used commercial (2-bromo and 2-chlorobenzaldehyde **25a,b**) or were prepared according to the procedures published in the literature.



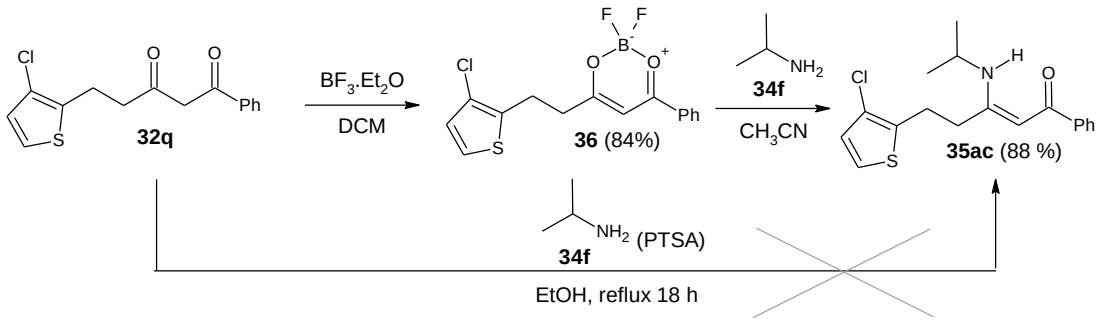
Scheme 1 Retrosynthetic analysis of the starting enaminones

*(Note: An exception was the synthesis of indole esters **30a,b** (serie D), for details see doctoral thesis)*

β-Diketones derived from pyrazoles (series C) were not successfully prepared. Almost all indole derivatives (series D) were extremely unstable and for that reason they were not subjected to Buchwald-Hartwig *N*-arylation.

Almost all desired enaminones **33a–r, 35a–ac** were obtained by the reaction of β-diketones **32a–t** with ammonium surrogate (NH_4OAc) or primary amine (methylamine **34a**,

cyclopropylamine **34b**, benzylamine **34c**, aniline **34d**, *p*-anisidine **34e**). In the case of sterically hindered *N*-isopropyl substituted enaminone **35ac**, pre-activation of β-diketone with boron trifluoride diethyl etherate was necessary prior to addition of isopropylamine to complete the reaction (Scheme 2).



Scheme 2 Preparation of the enaminone **35ac** with sterically demanding substituent on nitrogen

The regioselectivity of the synthesis of enaminones **33a–r, 35a–ac** was checked by means of 2D $^{1}H - ^{13}C$ HMBC, an example is given in Figure 4. There is a cross-peak indicating the interaction of quaternary carbon atom (~ 190 ppm) with aromatic protons (~ 7,87 ppm) in the spectrum showing the presence of benzoyl group in the molecule. The interaction of the quaternary carbon bearing amino group (~ 160 ppm) with the protons of methylene groups in aliphatic area is obvious as well.

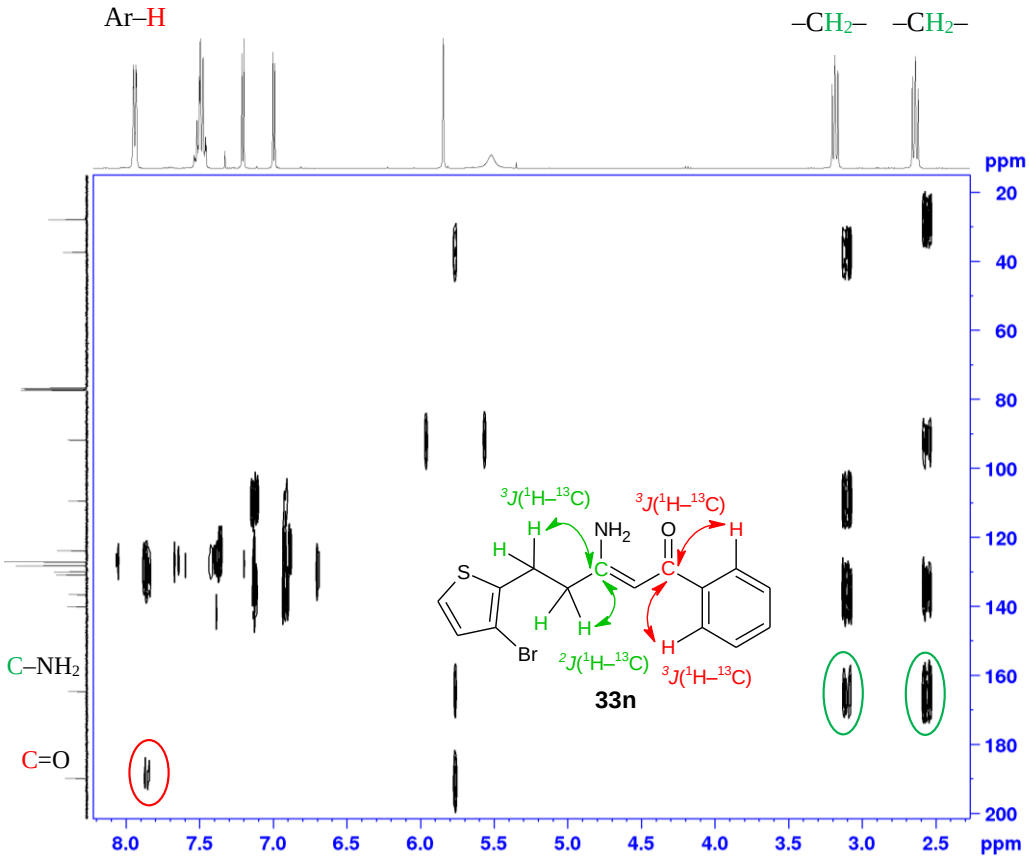


Figure 4 HMBC (400 MHz, $CDCl_3$) spectrum of enaminone **33n**

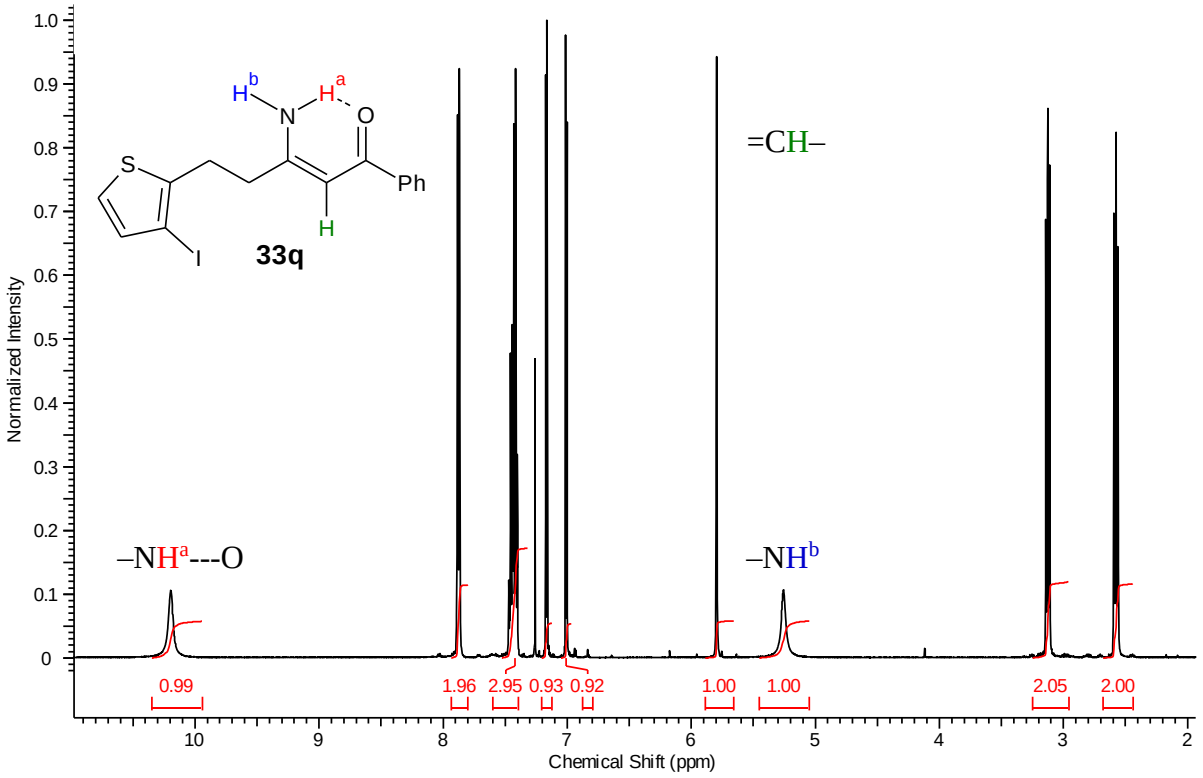


Figure 5 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of enaminone **33q**

The non-equivalence of NH_2 protons together with relatively high chemical shift of one resonance of the pair (δ ~ 10 ppm) indicate the presence of an intramolecular hydrogen bond N–H···O (Figure 5). Compounds **33a–r** therefore possessed *Z* configuration on the double bond. The situation was similar for *N*-substituted enaminones **35a–ac** (the presence of an intramolecular hydrogen bond). The structure of some enaminones was confirmed also in the solid state by X-ray diffraction (Figure 6).

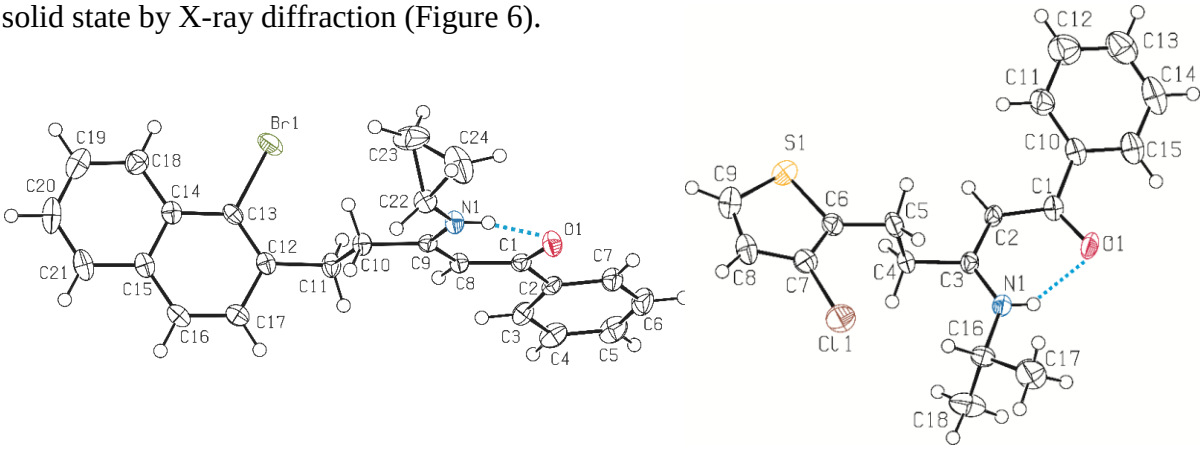
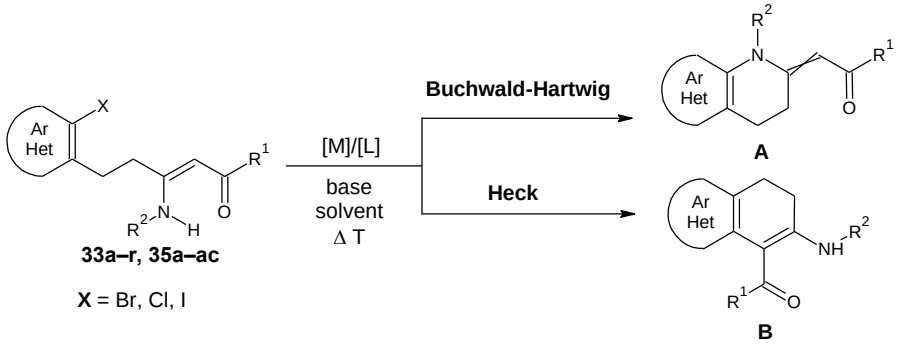


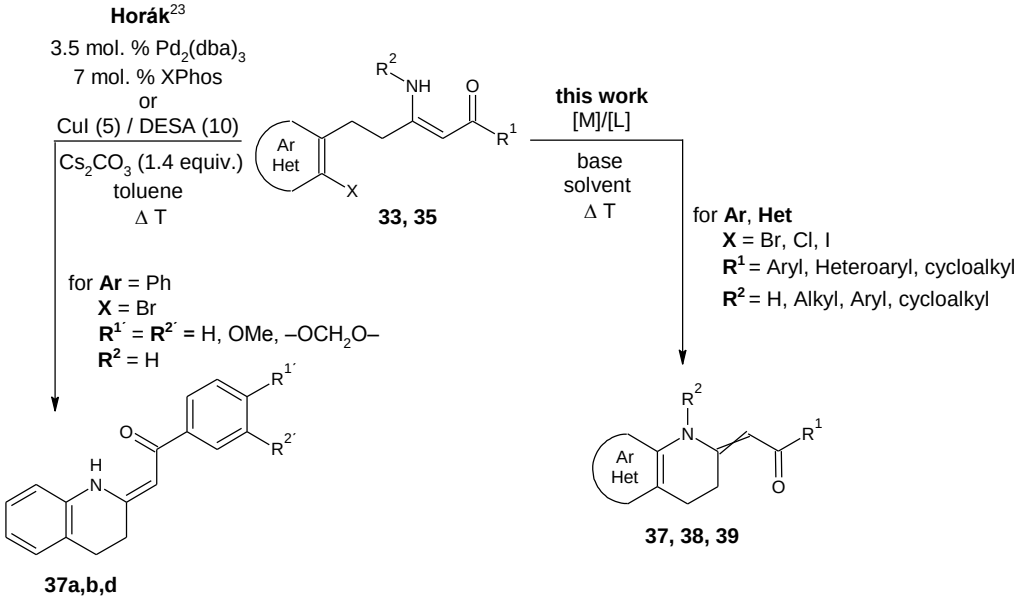
Figure 6 ORTEP diagrams of enaminones **35x** (left) and **35ac** (right)

2.2 Cyclization reaction



Scheme 3 Theoretical possibilities of an intramolecular CC reaction of enaminones **33a–r, 35a–ac**

The acyclic enaminones **33a–r, 35a–ac** were subjected to an intramolecular CC reaction under different catalytic conditions allowing formation of Buchwald-Hartwig cyclized products **A**. Theoretically, the structure of the starting substrates can provide Heck reaction products **B** (C-arylation of olefinic sp^2 carbon) as well (Scheme 3).



Scheme 4 Extension of the methodology – previous results vs this work

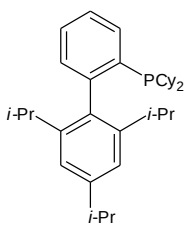
The first screening of the reaction conditions suitable for *N*-arylation of three bromo substituted enaminones with primary amino group was performed by Horák in his master thesis.[23] In the present doctoral thesis a large portfolio of other structurally different acyclic enaminones (Br-, Cl- and I-substituted enaminones with primary or secondary amino group) was cyclized under specific reaction conditions depending on the structure of the starting substrate (Scheme 4). A library of new tetrahydropyridine-based enaminones was prepared in manner of C–N CC.

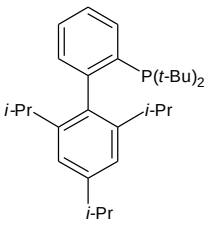
2.2.1 Optimization study

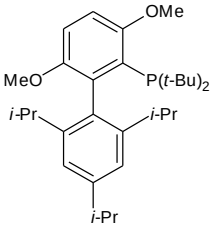
The reaction conditions for the intramolecular C–N CC of all the prepared acyclic enaminones **33**, **35** (0.5 mmol of a substrate was used in each experiment) were surveyed from the following aspects: catalysts, ligands, precatalysts, bases, solvents and reaction time. The ligands and precatalysts used in this work are listed below (Figure 7).

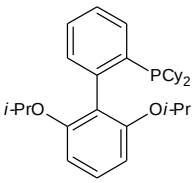
The stoichiometric ratio of the palladium source and the ligand [L] was always used 1:2 because formed $L_2Pd(0)$ is a thermodynamically stable 14-electron complex which is more active at higher temperature than a 16-electron complex LPd(0) which is formed when the ratio is 1:1;[Ref. 24] although the second mentioned complex was advantageously used by Hartwig for C–N CC at room temperature.[25]

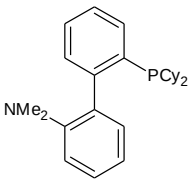
Biaryl Phosphine ligands

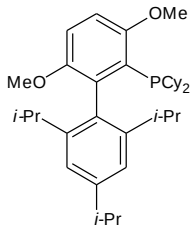

XPhos **(L1)**

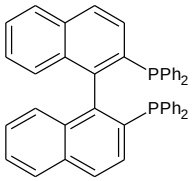

t-BuXPhos **(L2)**

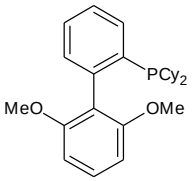

t-BuBrettPhos **(L3)**


RuPhos **(L4)**

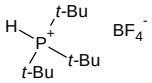

DavePhos **(L5)**


BrettPhos **(L6)**

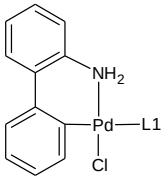

rac-BINAP **(L7)**

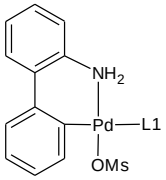

SPhos **(L8)**

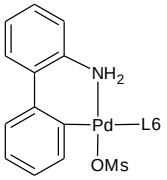
Trialkyl phosphonium salts

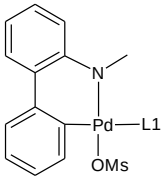

TTBP

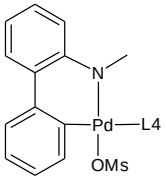
The 2nd, 3rd and 4th generation Buchwald precatalysts


PdG2 XPhos **(PdG2 L1)**

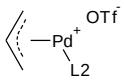

PdG3 XPhos **(PdG3 L1)**

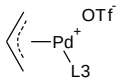

PdG3 BrettPhos **(PdG3 L6)**


PdG4 XPhos **(PdG4 L1)**


PdG4 RuPhos **(PdG2 L4)**

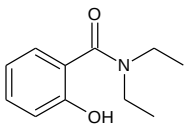
π-allylPd complexes

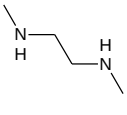

AllylPd(*t*-BuXPhos)(OTf) **(AllylPd L2(OTf))**


AllylPd(*t*-BuBrettPhos)(OTf) **(AllylPd L3(OTf))**


AllylPd(RuPhos)(Cl) **(AllylPd L4(Cl))**

Nitrogen-based ligands


DESA **(L9)**


DMEDA **(L10)**

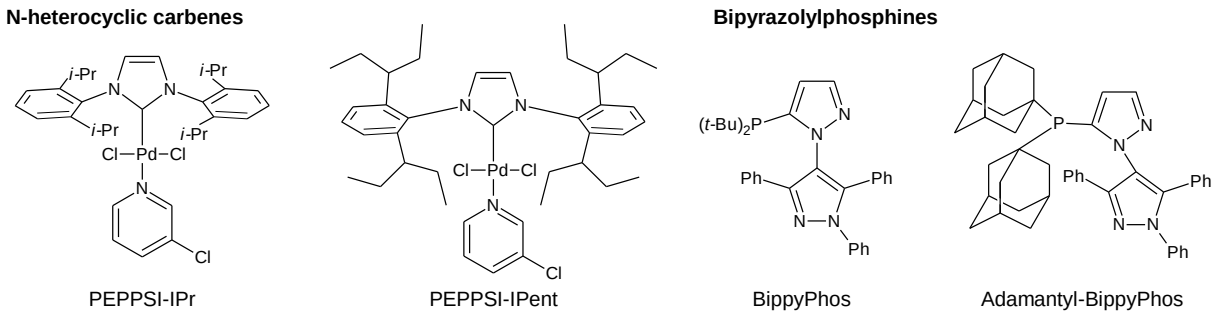


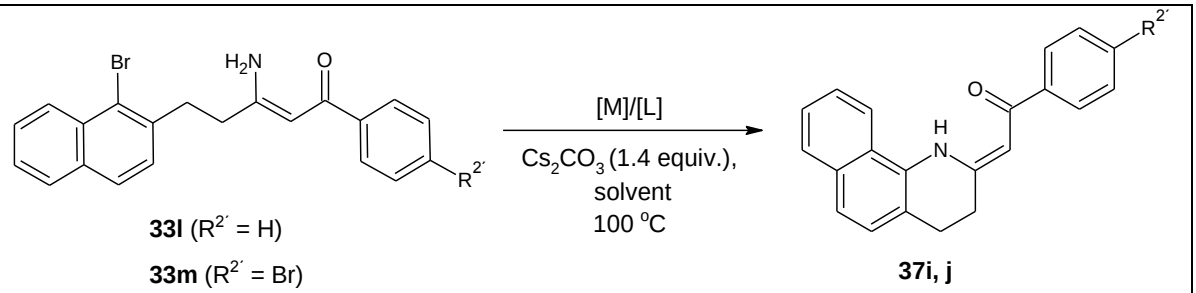
Figure 7 Ligands and precatalysts used in the doctoral thesis

2.2.1.1 Acyclic enaminones 33 with primary amino group

With the conditions previously found for some bromo derivatives (Scheme 4),[23] we followed up on the cyclization of naphthalene derivatives **33l, m**. The most suitable source of palladium for bromo substituted enaminones was $Pd_2(dba)_3$.[Ref. 22,23] To suppress the problems with the attenuation of its catalytic activity due to the coordination of dba ligands to the central metal, we applied preheating of $Pd_2(dba)_3$ with the corresponding ligand to generate active catalyst[26] prior to the addition to substrate. Dialkylbiarylphosphines L1–L8 currently belong among the most common ligands for palladium-catalyzed C–N CC.[Ref. 26,27] Although the use of 3.5 mol. % $Pd_2(dba)_3$ in combination with 7 mol. % XPhos (L1) worked well for some bromo substituted phenyl derivatives (Scheme 4),[22,23] the obtained results were insufficient in case of the naphthalene compound **33l** (Table 1, entry 1,2). A 50% conversion was obtained using relatively huge amount of the catalyst (up to 7.5 mol. %) and after a long period (3 d). The pure product **37i** was not isolated considering the high amount of the catalyst and relatively small amount of the product presented in the crude reaction mixture (complicated column chromatography). Changing the ligand to bidentate *rac*-BINAP (L7) or bulky *t*-BuBrettPhos (L3) significantly deteriorated the conversion (Table 1, entry 3–5). Since the traditional catalytic systems failed (Table 1, entry 1–5) we tested some modern palladium precatalysts (Table 1, entry 6–9) which have more benefits than their predecessors.[2,5,24,28,29] Those precatalysts, although having many advantages, for example, simpler reaction setup, often milder reaction conditions required and better reproducibility, are still rarely applied.[8] 2-Aminobiphenyl palladacycles are a class of widely used palladium precatalysts introduced by Buchwald´s group.[28,30,31] Four generations of the precatalysts (PdG1–4) have been describe to date. We applied the fourth generation of XPhos palladacycle PdG4 XPhos (L1) (Table 1, entry 6), owing to the problems associated with carbazole by-product, described for the third generation.[32] However, this catalytic system failed. Next, we trialed π-allylpalladium

t-BuXPhos (L2) and *t*-BuBrettPhos (L3) complexes (Table 1, entry 7, 8) introduced by Colacot´s group.[32] Unfortunately, they gave poor results too. Last precatalyst unsuccessfully applied to the naphthalene derivative **33l** was PEPPSI-IPent (PEPPSI = **p**yridine-**e**nhanced **p**recatalyst **p**reparation **s**tabilization and **i**nitiation) introduced by Organ´s group[29] (Table 1, entry 9). The copper catalysis failed as well (Table 1, entry 10, 11). Thus, an optimal reaction conditions for the cyclization of the naphthalene derivatives **33m, l** were not found, hence, these substrates still remain challenging.

Table 1 Optimization study for *N*-arylation of naphtalene derivatives **33l,m**



33l ($R^{2'}$ = H)

33m ($R^{2'}$ = Br)

37i, j

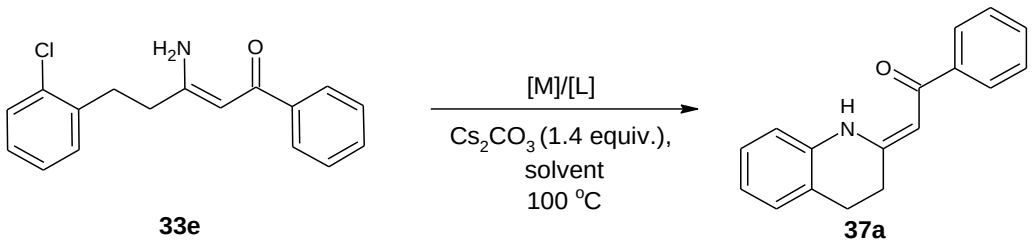
Entry (33l)	[M] (mol. %)	Ligand (mol. %)	Solvent (3 ml)	Reaction time (h)	Conversion[a] (%)
1	$Pd_2(dba)_3$ (5)	XPhos (10)	toluene	71	29
2	$Pd_2(dba)_3$ (7.5)	XPhos (15)	toluene	72	52
3	$Pd_2(dba)_3$ (5)	*rac*-BINAP (10)	toluene	70	7
4	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	toluene	70	5
5[b]	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	*t*-AmylOH	72	9
6	PdG4 XPhos (3)		toluene	72	0
7	AllylPd(*t*-BuXPhos)(OTf) (4) / *t*-BuXPhos (4)		*t*-AmylOH	20	0
8	AllylPd(*t*-BuBrettPhos)(OTf) (4)		*t*-AmylOH	70	7
9	PEPPSI-IPent (5)		*t*-AmylOH	72	0
10	CuI (10)	DESA (20)	toluene	71	0
11	CuI (10) / DESA (20) / KI (20)		toluene	70	5

*a) Determined by means of ^{1}H NMR of the crude reaction mixture; b) The same reaction conditions were applied to substrate **33m** with no conversion;*

Subsequently, our attention was focused on the cyclisation of chloro derivatives **33** with primary amino group. Although chloro substituted enaminones are relatively cheaper than their bromo substituted analogues, they are also less reactive. As the consequence, chloro derivatives are more challenging substrates for CC reactions. The enaminone **33e** was used as a model substrate. We started with the catalytic system $Pd_2(dba)_3$ / XPhos (L1) / Cs_2CO_3 / toluene successfully applied for bromo substituted phenyl derivatives,[22,23] but with an increased amount of palladium; 5 mol. % vs 3.5 mol. % (Table 2, entry 1). However, these conditions failed. Changing the ligand to *rac*-BINAP (L7) or DavePhos (L5) did not improve the situation at all (Table 2, entry 2, 3). The application of palladacycle-based precatalyst (PdG2 XPhos (L1)) was neither successful utilizing various solvents (Table 2, entry 4–7). A sterically more demanding

ligand BrettPhos (L6), reported as a very efficient ligand for *N*-arylations of primary amino groups,[26,33] worked better but was still not satisfactory (Table 2, entry 8). Bulkier *t*-BuBrettPhos (L3) did not worked at all (Table 2, entry 12). The breakthrough was made after applying *t*-BuXPhos (L2), which led to 64% conversion (Table 2, entry 9). Switching from toluene to *t*-AmylOH finally led to full conversion to the desired product **37a** after 17 h (Table 2, entry 10). Modern palladium precatalyst AllylPd(*t*-BuXPhos) (L2)(OTf) combined with another equivalent of *t*-BuXPhos (L2) (Table 2, entry 13) was unsuccessful. The copper-catalyzed protocol was quite ineffective. (Table 2, entry 14). Generally, chloro derivatives (and especially non-activated ones) remain challenging substrates for copper catalysis.[34] The best conditions for *N*-arylation of chloro derivative **33e** were thus $Pd_2(dba)_3$ (5 mol. %) / *t*-BuXPhos (L2) (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH (Table 2, entry 10).

Table 2 Optimization study for *N*-arylation of chloro derivative **33e**



33e **37a**

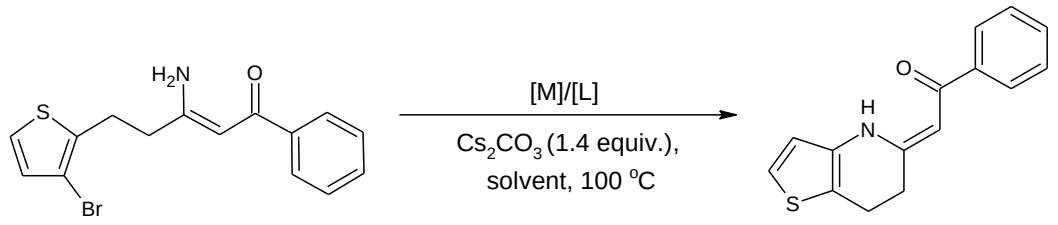
Entry (33e)	[M] (mol. %)	Ligand (mol. %)	Solvent (3 ml)	Reaction time (h)	Conversion[a]/ Isolated yield (%)
1	$Pd_2(dba)_3$ (5)	XPhos (10)	toluene	48	0/-
2	$Pd_2(dba)_3$ (5)	*rac*-BINAP (10)	toluene	24	0/-
3	$Pd_2(dba)_3$ (5)	DavePhos (10)	toluene	24	0/-
4[b]	PdG2 XPhos (3)		toluene	24	0/-
5[b]	PdG2 XPhos (3)		*n*-AmylOH	24	0/-
6[b]	PdG2 XPhos (3)		DMF	24	4/-
7[b]	PdG2 XPhos (3)		*t*-AmylOH	24	0/-
8	$Pd_2(dba)_3$ (5)	BrettPhos (10)	toluene	22	29/-
9	$Pd_2(dba)_3$ (5)	*t*-BuXPhos (10)	toluene	22	64/-
10	**$Pd_2(dba)_3$ (5)**	***t*-BuXPhos (10)**	***t*-AmylOH**	**17**	**>99/72**
11	$Pd_2(dba)_3$ (2.5)	*t*-BuXPhos (5)	*t*-AmylOH	24	47/-
12	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	*t*-AmylOH	48	8/-
13	AllylPd(*t*-BuXPhos)(OTf) (4) / *t*-BuXPhos (4)		*t*-AmylOH	48	6/-
14	CuI (10)	DESA (20)	toluene	24	0/-

a) Determined by means of ^1H NMR of the crude reaction mixture; b) Two equivalents of the base used.

Heteroaryl halides are often difficult substrates for Buchwald-Hartwig amination owing to their specific electronic properties[35–37] (electron-rich heteroaryl ring retards nucleophilic substitution of a halide). At the following stage of our study, we attempted to find the conditions for the cyclization of thiophene derivatives **33n–q** halogenated on the heterocyclic moiety.

We started our optimization study with the cyclization of bromo derivative **33n**. Within the traditional catalytic systems (Table 3, entry 1–3), the best results were obtained using the bulky *t*-BuBrettPhos (L3) in *t*-AmylOH (Table 3, entry 3). The 3rd and 4th generation Buchwald preformed precatalysts failed (Table 3, entry 4, 5) as well as PEPPSI-IPr ((Table 3, entry 7). Since *t*-BuBrettPhos (L3) worked best, the precatalyst AllylPd(*t*-BuBrettPhos) (L3)(OTf) was prepared[32] and tested (Table 3, entry 6). However, no conversion was observed. The copper-catalyzed protocol using DESA (L9) which can be used for bromophenyl derivatives was ineffective here (Table 3, entry 8). The copper-catalysis variation consisted of the use of KI (Table 3, entry 9) which transform the starting bromide to iodide as a better leaving group, led to higher conversion, albeit insufficient.

Table 3 Optimization study for *N*-arylation of bromo thiophene **33n**



33n **38a**

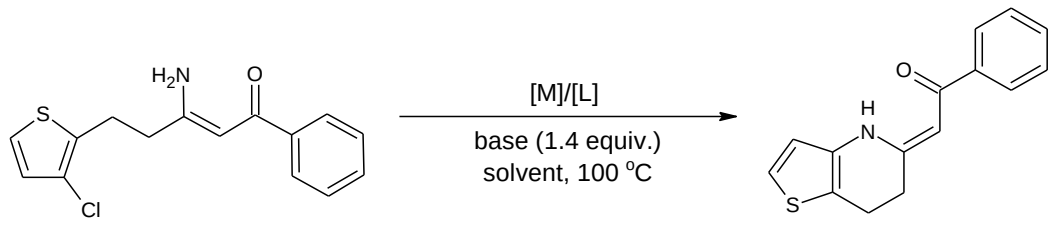
Entry (33n)	[M] (mol. %)	Ligand (mol. %)	Solvent (3 ml)	Reaction time (h)	Coversion[a] / Isolated yield (%)
1	$Pd_2(dba)_3$ (5)	XPhos (10)	toluene	48	0
2	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	toluene	72	41
3	**$Pd_2(dba)_3$ (5)**	***t*-BuBrettPhos (10)**	***t*-AmylOH**	**45**	**87/72**
4	PdG3 XPhos (10) / XPhos (10)		toluene	48	0
5	PdG4 XPhos (3)		*t*-AmylOH	48	0
6	AllylPd(*t*-BuBrettPhos)(OTf) (4)		*t*-AmylOH	66	0
7	PEPPSI-IPr (10)		*t*-AmylOH	67	0
8	CuI (10)	DESA (20)	toluene	72	8
9	CuI (10) / DESA (20) / KI (20)		toluene	46	28

a) Determined by means of ^1H NMR of the crude reaction mixture;

The optimization study for chlorothiophene derivative **33p** is expressed in Table 4. The most efficient catalytic system was the same as for bromothiophene **33n**; $Pd_2(dba)_3$ / *t*-BuBrettPhos (L3) / Cs_2CO_3 / *t*-AmylOH (Table 4, entry 5). The results obtained with the catalytic system successful in the case of chlorophenyl derivative **33e** were inferior here (Table 4, entry 1). Switching the base to K_3PO_4 or solvent to DMF did not help (Table 4, entry 3, 4). The ligand SPhos (L8) with stronger base *t*-BuONa was used for the amination of halogenated thiophenes in lit.[26,37] but in our case no conversion was detected (Table 4, entry 2). In another experiment, a stable preformed trialkylphosphonium salt,[38] $(t\text{-Bu})_3P^+HBF_4^-$, was tested with no satisfactory results (Table 4, entry 7). Amination of heteroarylchlorides was also

accomplished with BippyPhos.[39] This type of the ligand inhibits β-hydride elimination which is often problematic for electron-rich hetero/arylhalides.[40] Only about 20% conversion was observed in our case (Table 4, entry 8, 9). Water-mediated palladium acetate based protocol for generation of the highly active Pd(0) described by Buchwald et al.[41] failed (Table 4, entry 10, 11).

Table 4 Optimization study for *N*-arylation of chloro thiophene **33p**



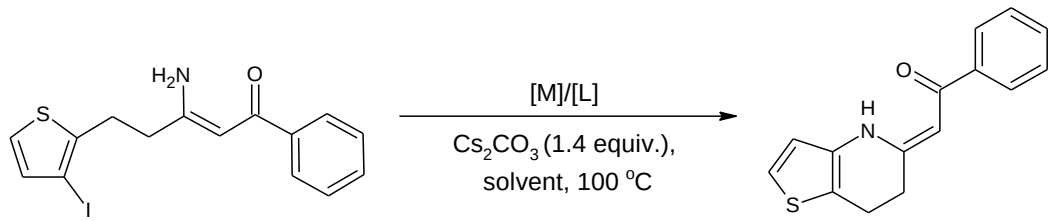
33p **38a**

Entry (33p)	[M] (mol. %)	Ligand (mol. %)	Base	Solvent (3 ml)	Reaction time (h)	Conversion[a] / Isolated yield (%)
1	$Pd_2(dba)_3$ (5)	*t*-BuXPhos	Cs_2CO_3	*t*-AmylOH	48	34/30
2	$Pd_2(dba)_3$ (5)	SPhos (10)	*t*-BuONa	toluene	48	0
3	$Pd_2(dba)_3$ (5)	*t*-BuXPhos (10)	Cs_2CO_3	DMF	72	0
4	$Pd_2(dba)_3$ (5)	*t*-BuXPhos (10)	K_3PO_4	*t*-AmylOH	70	20
5	**$Pd_2(dba)_3$ (5)**	***t*-BuBrettPhos (10)**	**Cs_2CO_3**	***t*-AmylOH**	**71**	**85/71**
6	$Pd_2(dba)_3$ (5)	*rac*-BINAP	Cs_2CO_3	*t*-AmylOH	70	0
7	$Pd_2(dba)_3$ (5)	$(t\text{-Bu})_3P^+HBF_4^-$ (10)	Cs_2CO_3	*t*-AmylOH	70	0
8	$Pd_2(dba)_3$ (5)	BippyPhos (di*t*-Bu) (10)	Cs_2CO_3	*t*-AmylOH	72	20
9	$Pd_2(dba)_3$ (5)	BippyPhos (adamantyl) (10)	Cs_2CO_3	*t*-AmylOH	72	23
10	$Pd(OAc)_2$ (5)	*t*-BuXPhos (15)	Cs_2CO_3	*t*-AmylOH	48	0
11	$Pd(OAc)_2$ (5)	*t*-BuBrettPhos (15)	Cs_2CO_3	*t*-AmylOH	72	9

a) Determined by means of ^1H NMR of the crude reaction mixture; b) Water-mediated pre-activation (2 ml t-AmylOH + 1,8 µl water)

Furthermore, the successful conditions for *N*-arylation of bromo and chloro substituted thiophenes **33n, p** were applied to iodo derivative **33q** (Table 5, entry 1). Surprisingly, the reaction did not proceed. On the other hand, almost quantitative conversion was reached using copper-catalysis (Table 5, entry 2).

Table 5 Optimization study for *N*-arylation of iodo thiophene **33q**



33q **38a**

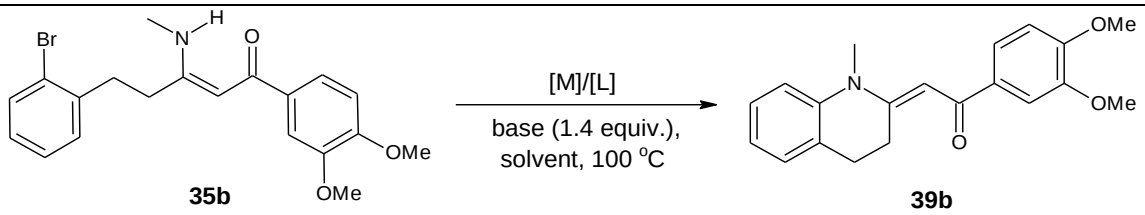
Entry (33n)	[M] (mol. %)	Ligand (mol. %)	Solvent (3 ml)	Reaction time (h)	Conversion[a] (%)
1	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	*t*-AmylOH	72	0
2	**CuI (10)**	**DESA (20)**	**toluene**	**24**	**>99**

a) Determined by means of ^1H NMR of the crude reaction mixture;

2.2.1.2 Acyclic enaminones 35 with secondary amino group

The cyclization of haloaryl enaminones **35** with secondary amino group was optimized on the compound **35b**. RuPhos (L4; Figure 7) is well known to be an effective ligand for palladium-catalyzed amination of secondary amino derivatives.[26,33] It was therefore the ligand of choice in this part of our study.

Table 6 Optimization study for *N*-arylation of **35b**



35b **39b**

Entry (35b)	[M] (mol. %)	Ligand (mol. %)	Base	Solvent (3 ml)	Reaction time (h)	Conversion[a] / Isolated yield (%)
1	$Pd_2(dba)_3$ (5)	RuPhos (10)	Cs_2CO_3	*t*-AmylOH	24	44/15
2	**$Pd_2(dba)_3$ (5)**	**RuPhos (10)**	**Cs_2CO_3**	**DMF**	**24**	**>99/87**
3	$Pd_2(dba)_3$ (5)	RuPhos (10)	K_3PO_4	DMF	24	0
4	$Pd_2(dba)_3$ (5)	RuPhos (10)	K_2CO_3	DMF	24	0
5[b]	PdG3 BrettPhos (3)		Cs_2CO_3	*t*-BuOH	24	0
6	AllylPd(RuPhos)(Cl) (2) / RuPhos (2)		Cs_2CO_3	DMF	24	4

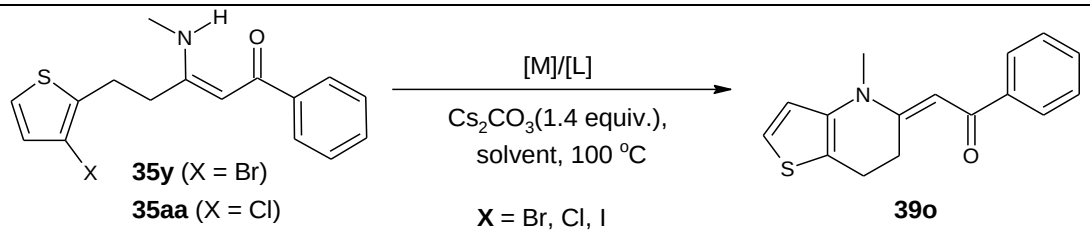
a) Determined by means of ^1H NMR of the crude reaction mixture; b) Reaction proceeded at 80 °C

Solvent appeared to be a crucial factor here, as the change from *t*-AmylOH to DMF brought about a considerable increase in the conversion (Table 6, entry 1, 2). An attempt to replace the base Cs_2CO_3 with cheaper K_3PO_4 or K_2CO_3 led to 0% conversion to product **39b** (Table 6, entry 3, 4). The application of π-allylpalladium RuPhos (L4) complex was not useful (Table 6, entry 6). The 3rd generation Buchwald precatalyst containing BrettPhos (L6) which was published as highly effective for *N*-arylation of primary and secondary amino derivatives (in some cases 0.01 mol. % was sufficient)[30] failed as well (Table 6, entry 5). Traditional catalytic

system (Table 6, entry 2) was again the most appropriate one for bromo derivative **35b**. We also obtained satisfactory results with this catalytic system for chlorophenyl derivative **35m** (72 h, 83% conversion; 71% yield) thus it was not necessary to carry on further optimization.

Finally, 3-halothiophene derivatives **35y–ab** were examined. The results are summarized in Table 7.

Table 7 Optimization study for *N*-arylation of **35y–ab**



Entry (substrate)	[M] (mol. %)	Ligand (mol. %)	Solvent (3 ml)	Reaction time (h)	Conversion[a] / Isolated yield (%)
1 (**35y**)	$Pd_2(dba)_3$ (5)	RuPhos (10)	DMF	65	33
2 (35y)	**$Pd_2(dba)_3$ (5)**	**RuPhos (10)**	***t*-AmylOH**	**68**	**>99/63**
3 (**35y**)	$Pd_2(dba)_3$ (5)	*t*-BuBrettPhos (10)	*t*-AmylOH	72	0
4 (**35y**)	PdG4 RuPhos (3)		*t*-AmylOH	72	0
5 (**35y**)	AllylPd(RuPhos)(Cl) (2)		*t*-AmylOH	72	18
6 (**35y**)	AllylPd(RuPhos)(Cl) (4)		*t*-AmylOH	72	63
7 (**35y**)	AllylPd(RuPhos)(Cl) (2) / RuPhos (2)		*t*-AmylOH	72	30
8 (35y)	**AllylPd(RuPhos)(Cl) (4) / RuPhos (4)**		***t*-AmylOH**	**72**	**>99**
9 (**35y**)	AllylPd(RuPhos)(Cl) (4) / RuPhos (4)		*t*-AmylOH	2	18
10 (**35y**)	AllylPd(*t*-BuXPhos)(OTf) (4)		*t*-AmylOH	70	0
11 (**35y**)	PEPPSI-IPr (10)		*t*-AmylOH	70	0
12 (**35aa**)	$Pd_2(dba)_3$ (5)	RuPhos (10)	DMF	70	9
13 (35aa)	**$Pd_2(dba)_3$ (5)**	**RuPhos (10)**	***t*-AmylOH**	**42**	**74/52**
14 (**35aa**)	AllylPd(RuPhos)(Cl) (4) / RuPhos (4)		*t*-AmylOH	71	0
15 (**35ab**)	$Pd_2(dba)_3$ (5)	RuPhos (10)	*t*-AmylOH	70	0
16 (35ab)	**AllylPd(RuPhos)(Cl) (4) / RuPhos (4)**		***t*-AmylOH**	**48**	**>99**
17 (**35ab**)	CuI (10)	DESA (20)	toluene	66	0
18 (**35ab**)	CuI (10)	DMEDA (20)	toluene	65	0

a) Determined by means of ^1H NMR of the crude reaction mixture;

The above-mentioned screening of many catalytic systems revealed two optimal reaction conditions for bromo derivative **35y**. The comparable results were obtained using $Pd_2(dba)_3$ / RuPhos (L4) / Cs_2CO_3 / *t*-AmylOH (Table 7, entry 2) or AllylPd(RuPhos)(Cl) (4) / RuPhos (L4) (4) (Table 7, entry 8). First attempt with smaller amount of π-allylpalladium RuPhos (L4) complex (2 mol. %) gave only 18% conversion (Table 7, entry 5). The higher amount (4 mol. %) of RuPhos (L4) complex worked better (Table 7, entry 6) but an addition of another equivalent of RuPhos (L4) brought about a significant improvement (Table 7, entry 8). These conditions are universal also for iodo derivative **35ab** (Table 7, entry 8, 16). On the other

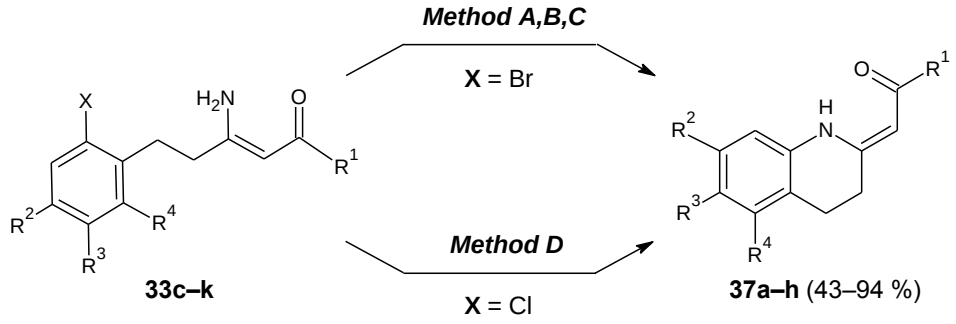
hand, the conventional system work for both the bromo and chloro substituted enaminones **35y, aa** (Table 7, entry 2, 13).

2.2.2 Synthesis and characterization

A library of tetrahydroquinolines **37, 39** and tetrahydrothienopyridines **38, 39** and one dihydrobenzothiophene **40** was prepared under the conditions resulting from the above-mentioned optimizations (Table 1–7) depending on the structure of the starting acyclic enaminones **33, 35**.

2.2.2.1 Tetrahydroquinolines 37a–h unsubstituted on nitrogen

Table 8 An overview of the prepared tetrahydroquinolines **37a–h**

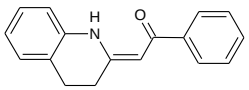
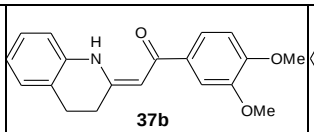
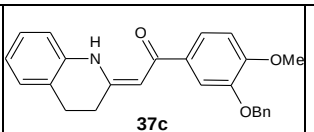
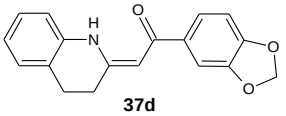
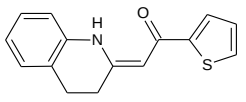
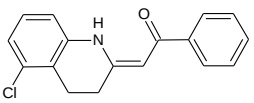
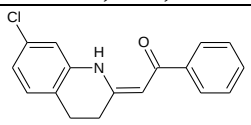
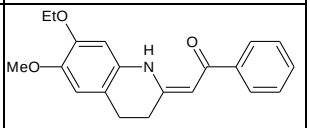


Method A: $Pd_2(dba)_3$ (5 mol. %) / XPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / toluene / 100 °C

Method B: $Pd_2(dba)_3$ (5 mol. %) / *t*-BuBrettPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH / 100 °C

Method C: CuI (10 mol. %) / DESA (20 mol. %) / Cs_2CO_3 (1.4 equiv.) / toluene / 100 °C

Method D: $Pd_2(dba)_3$ (5 mol. %) / *t*-BuXPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH / 100 °C

 **37a**	 **37b**	 **37c**	 **37d**
X = Cl: ***Method D***; 17 h, >99/72	X = Cl: ***Method D***; 20 h, >99/72	X = Br: ***Method A***; 2 h, >99/85 [a]***Method A***; 24 h, 52/43 X = Cl: ***Method D***; 19 h, >99/82	X = Cl: ***Method D***; 20 h, 68/61
 **37e**	 **37f**	 **37g**	 **37h**
X = Br; ***Method A***; 18 h, 85/55 ***Method B***; 18 h, >99/90 ***Method C***; 18 h, >99/94	X = Br; ***Method A***; 70 h, >99/78 ***Method D***; 71 h, >99/85 ***Method C***; 46 h, 25/-	X = Br; ***Method A***; 72 h, 38/- ***Method B***; 16 h, >99/73 ***Method C***; 72 h, >99/80	X = Br; ***Method B***; 18 h, >99/71

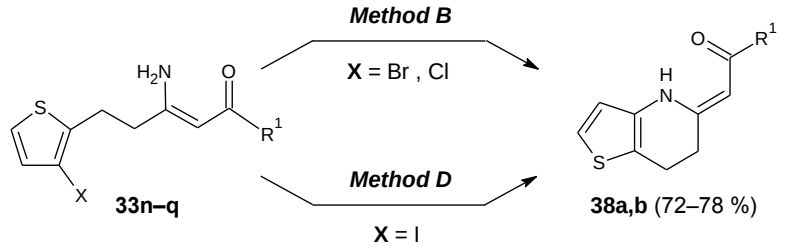
a) Modificated method used: $Pd_2(dba)_3$ (3.5 mol. %) / XPhos (7 mol. %) / Cs_2CO_3 (1.4 equiv.) / toluene / 100 °C;

Variously substituted tetrahydroquinolines **37a–h** were prepared from both bromo and chlorophenyl derivatives **33a–k** depicted in Table 8. The conditions, previously found for the

cyclization of three selected bromophenyl derivatives[22,23] ($Pd_2(dba)_3$ (3.5 mol. %) / XPhos (L1) (7 mol. %) / Cs_2CO_3 (1.4 equiv.) / toluene / 110 °C, 2 h) were not sufficient in the case of benzyloxy substituted enaminone **33c** (R^1 = 3-OBn-4-OMePh; $R^2 = R^3 = R^4$ = H, X = Br). After 24 h the conversion to **37c** was only 52 %. Hence, it was necessary to increase the amount of palladium (5 mol. %) to accomplish full conversion in comparable time (2 h). Similar situation occurred for 1-bromo-6-chlorosubstituted substrate **33i** (R^1 = Ph; $R^2 = R^3$ = H, R^4 = Cl, X = Br) when the full conversion was achieved after longer period (70 h). For 1-bromo-4-chlorosubstituted substrate **33j** (R^1 = Ph; R^2 = Cl, $R^3 = R^4$ = H, X = Br) reaction proceeded 72 h to reach only 38% conversion. Ligand XPhos (L1) was not successful enough also in the case of heteroaryl enaminone **33d** (R^1 = thiophene-2-yl; $R^2 = R^3 = R^4$ = H, X = Br). Therefore, the cyclization of **37e, g, h** was carried out under the conditions suitable for more challenging 3-halothiophene substrates **33n, p** (see chapter Optimization study; Tables 3, 4) using *t*-BuBrettPhos (L3) as the ligand (*Method B*). Quantitative conversion was then achieved for all the prepared bromo phenyl derivatives in relatively short reaction time (16–18 h) and the products were isolated in high yields (71–90 %). Copper-catalyzed variant (*Method C*) was advantageously used for some bromo derivatives (**37e, g**). Chloro derivatives **33e–h** afforded desired products **37a–d** using *t*-BuXPhos (L2) (*Method D*) in 17–20 h in moderate-to-high yields (61–82 %). Polysubstituted substrates **33i–k** (R^2, R^3, $R^4 \neq$ H) had more specific demands for the choice of a catalytic system (Table 8; **37f–h**).

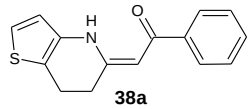
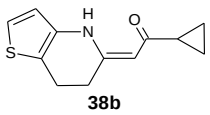
2.2.2.2 Tetrahydrothienopyridines 38a,b unsubstituted on nitrogen

Table 8 An overview of the prepared tetrahydrothienopyridines **38a,b**



Method B: $Pd_2(dba)_3$ (5 mol. %) / *t*-BuBrettPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH / 100 °C

Method C: CuI (10 mol. %) / DESA (20 mol. %) / Cs_2CO_3 (1.4 equiv.) / toluene / 100 °C

 **38a**	X = Br: ***Method B***; 45 h, 87/72 X = Cl: ***Method B***; 71 h, 85/74 X = I: ***Method C***; 24 h, >99/-
 **38b**	X = Br: ***Method B***; 42 h, >99/78

Thiophene derivatives **33n–p** bearing bromine or chlorine atom in position 3- were cyclized under the same conditions (*Method B*) providing products **38a, b** in 72–78 % yield. Longer

reaction time was required for chloro derivative **33p** (R^1 = Ph) to achieve comparable conversion. (**38a**; 45 h vs 72 h, Table 8). If R^1 was cyclopropyl the reaction proceeded faster (full conversion in 42 h) probably due to less steric demands. The amination of iodo derivative **33q** run quantitatively in shorter time (24 h) using the catalytic system CuI / DESA (L9) (*Method C*).

Characterization

On the basis of relatively high chemical shifts of NH protons in all tetrahydropyridines **37a, h, 38a, b** unsubstituted on nitrogen ($\delta > 12$), it can be assumed that all these compounds have *Z* configuration on the C=C double bond (increased chemical shifts due to the presence of an intramolecular hydrogen bond C=O···H–N). This assumption was also confirmed in the solid state by means of X-ray diffraction (Figure 8).

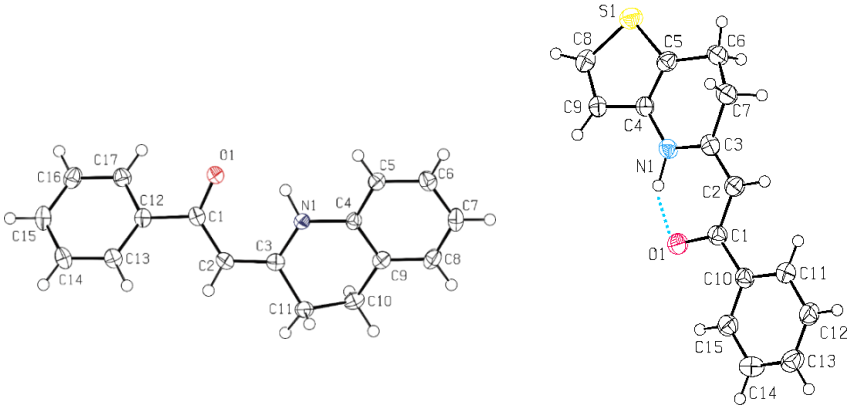
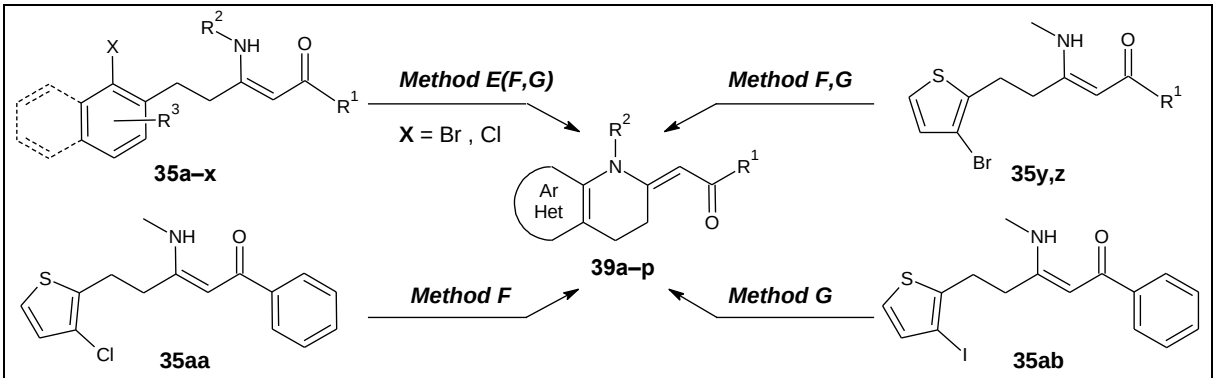


Figure 8 ORTEP diagrams of tetrahydropyridines **37a** (left) and **38a** (right)

2.2.2.3 Tetrahydropyridines 39a–p substituted on nitrogen

The synthesis of tetrahydropyridines **39a–p** variously substituted on the nitrogen was accomplished according to Table 9 using *Methods E–G*. In all the cases, CC reaction was palladium-catalyzed including ligand RuPhos (L4). A universally applicable catalytic system $Pd_2(dba)_3$ (5 mol. %) / RuPhos (L4) (10 mol. %) / Cs_2CO_3 (1.4 equiv.) (*Methods E, F)* was effective for all the enaminones **35a–aa** with secondary amino group except for iodothiophene derivative **35ab**. If the starting 2-halophenyl derivative **35a–u** was not polysubstituted (R^3 = H), the reaction proceeded better in DMF (one exception was the preparation of **39m**) (*Method E*). The synthesis of cyclic enaminones with condensed benzene ring (**39n**) or with alkoxy disubstitution (**39l**) was carried out in *t*-AmylOH, because the reaction in DMF led to low conversion (**39n**; Table 9, *Method E*) or did not proceed at all (**39l**).

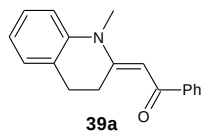
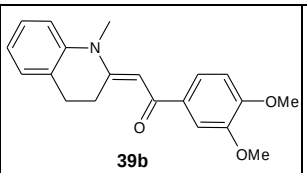
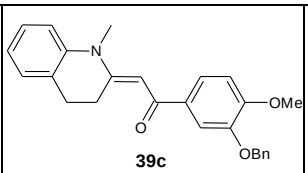
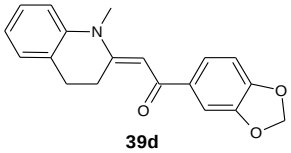
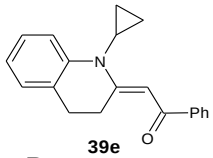
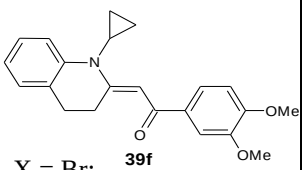
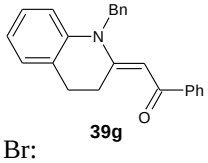
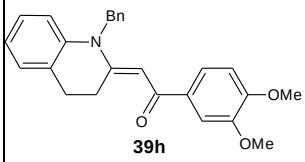
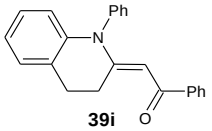
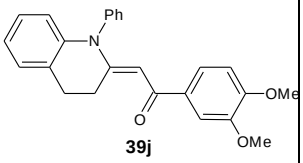
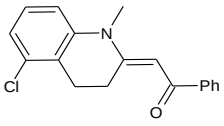
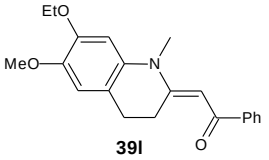
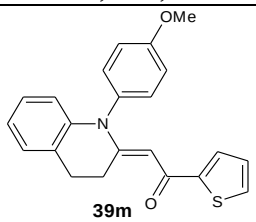
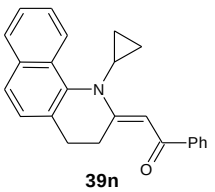
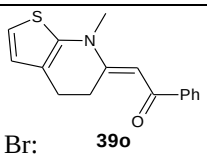
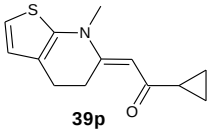
Table 9 An overview of the prepared tetrahydropyridines **39a–p**



Method E: $Pd_2(dba)_3$ (5 mol. %) / RuPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / DMF / 100 °C

Method F: $Pd_2(dba)_3$ (5 mol. %) / RuPhos (10 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH / 100 °C

Method G: AllylPd(RuPhos) (4 mol. %) RuPhos (4 mol. %) / Cs_2CO_3 (1.4 equiv.) / *t*-AmylOH / 100 °C

 **39a** X = Br: ***Method E***; 20 h, >99/89 ***Method F***; 24 h, 44/15 X = Cl: ***Method E***; 24 h, >99/80	 **39b** X = Br: ***Method E***; 24 h, >99/87 X = Cl: ***Method E***; 72 h, 83/71	 **39c** X = Br: ***Method E***; 22 h, >99/81 X = Cl: ***Method E***; 72 h, 85/62	 **39d** X = Br: ***Method E***; 19 h, >99/81 X = Cl: ***Method E***; 42 h, 99/82
 **39e** X = Br: ***Method E***; 20 h, >99/89 X = Cl: ***Method E***; 24 h, >99/83	 **39f** X = Br: ***Method E***; 23 h, >99/65 X = Cl: ***Method E***; 46 h, 83/70	 **39g** X = Br: ***Method E***; 44 h, >99/86 X = Cl: ***Method E***; 44 h, >99/96	 **39h** X = Br: ***Method E***; 42 h, >99/64 X = Cl: ***Method E***; 67 h, >99/82
 **39i** X = Br: ***Method E***; 42 h, >99/85 X = Cl: ***Method E***; 72 h, 84/60	 **39j** X = Br: ***Method E***; 20 h, >99/82 X = Cl: ***Methoda E***; 72 h, >99/80	 **39k** X = Br: ***Method E***; 72 h, 46/34	 **39l** X = Br: ***Method F***; 70 h, >99/82
 **39m** X = Br: ***Method F***; 68 h, >99/81 ***Method G***; 47 h, >99/86	 **39n** X = Br: ***Method E;*** 72 h, 47/- ***Method F***; 20 h, >99/72 ***Method G***; 20 h, >99/75	 **39o** X = Br: ***Method F***; 68 h, >99/63 ***Method G***; 72 h, >99/- X = Cl: ***Method F***; 42 h, 74/52 X = I: ***Method G***; 48 h, >99/-	 **39p** X = Br: ***Method F***; 48 h, >99/84 ***Method G***; 69 h, >99/86

It should be mentioned that the situation was opposite in model substrate **35b** (R^1 = Ph, R^2 = Me, R^3 = H, X = Br) (see Optimization study, Table 6, entry 1). Using modern RuPhos (L4) allylpalladium complex was not successful in model substrate **35b** (*Method G*). Thus, the best choice of the catalytic system depends mainly on the substitution R^3 and R^1. There was almost no influence of the substituent R^2 (on the nitrogen) on conversion. Generally, chloro derivatives **35l–u** needed longer reaction time to complete the reaction than their bromo analogues **35a–j**. Only 46% conversion to **39k** was reached after 72 h (*Method E*) in the case of 1-bromo-6-chloro-substituted starting substrate **35v** probably due to its electronic and/or steric properties.

Characterization

The structures of all the prepared enaminones **39a–p** were verified. Nuclear Overhauser effect spectroscopy (Figure 9) revealed *E* configuration on their exocyclic double bond which was also confirmed in the solid state by X-ray (Figure 10). It is an opposite to their NH analogues.

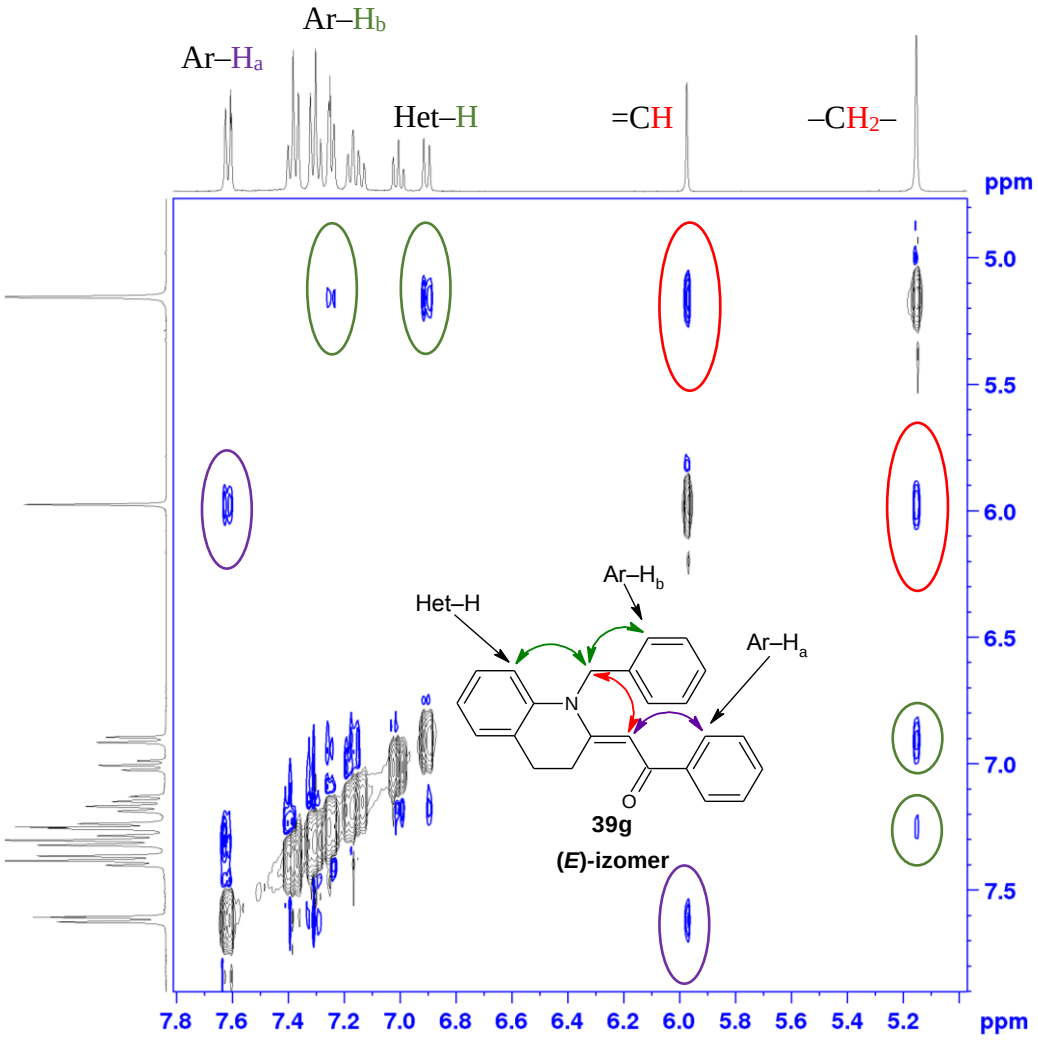


Figure 9 2D NOESY spectrum of **39g** in $CDCl_3$ (400 MHz, mixing time 800 ms)

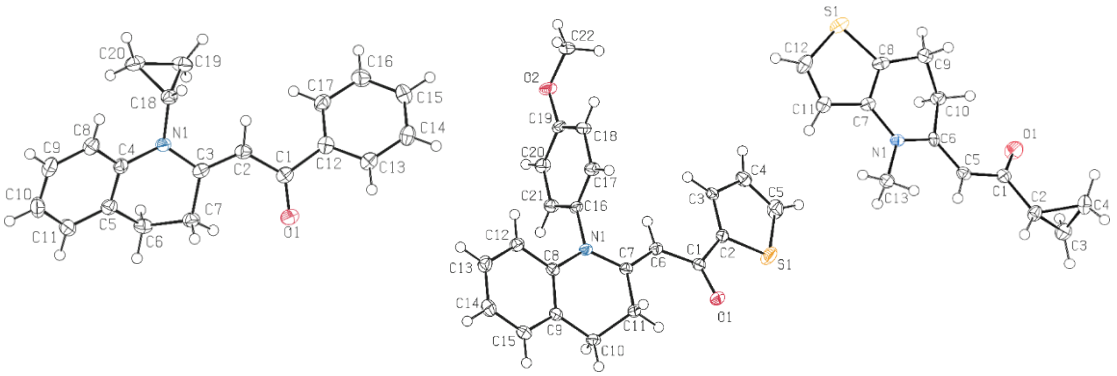
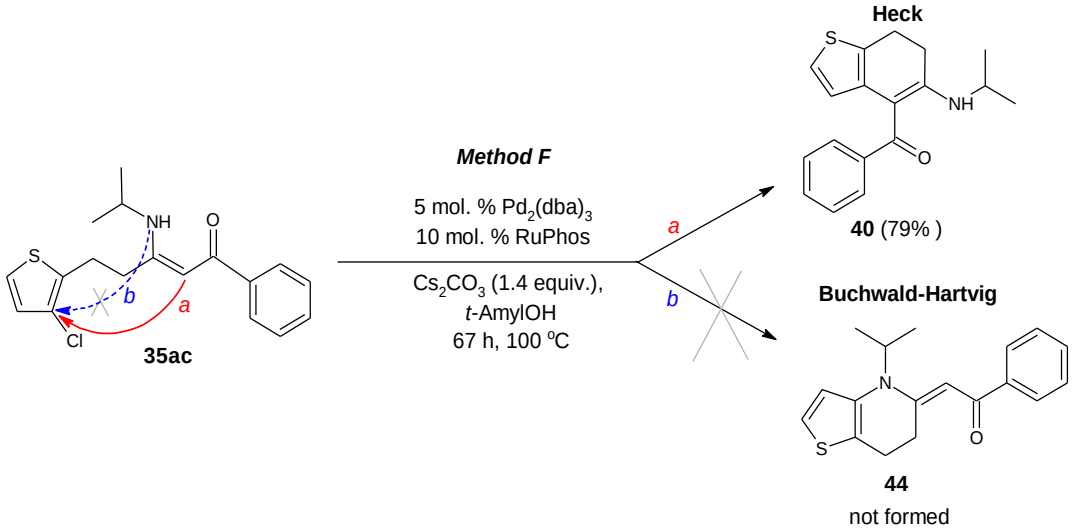


Figure 10 ORTEP diagrams of tetrahydropyridines **39e, m, p** (from left to right)

2.2.2.4 Competitive Heck reaction

Surprisingly, on attempt to cyclize the enaminone **35ac** containing *iso*propylamino group to give corresponding tetrahydropyridine **44**, an isomeric product **40** with distinct NMR spectrum was separated (Scheme 5). Although, this is the only case when the Heck-type product was isolated, it can be assumed that both Buchwald-Hartwig and Heck-type products are presented in the crude reaction mixture.



Scheme 5 Anomalous behavior against palladium-catalysis observed for **35ac**

Characterization

The absence of olefinic CH proton and the presence of NH proton signal in ^{1}H NMR spectra of **40** together with correlation spectroscopy and Nuclear Overhauser effect experiments confirmed the structure of the product as **40**. The presence of –NHCH$(CH_3)_2$ arrangement was obvious from COSY spectrum (Figure 11) and NOESY spectrum (Figure 12) revealed an interaction of the protons of *iso*propyl group with the protons of methylene belonging to the bicyclic molecule.

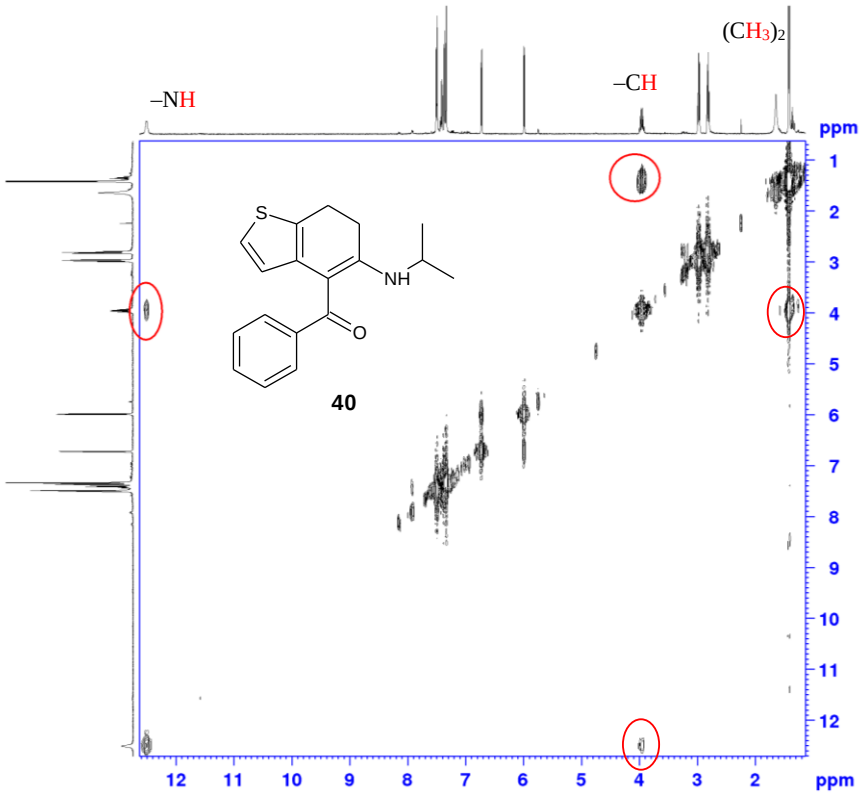


Figure 10 COSY spectrum of **40** in $CDCl_3$ (400 MHz)

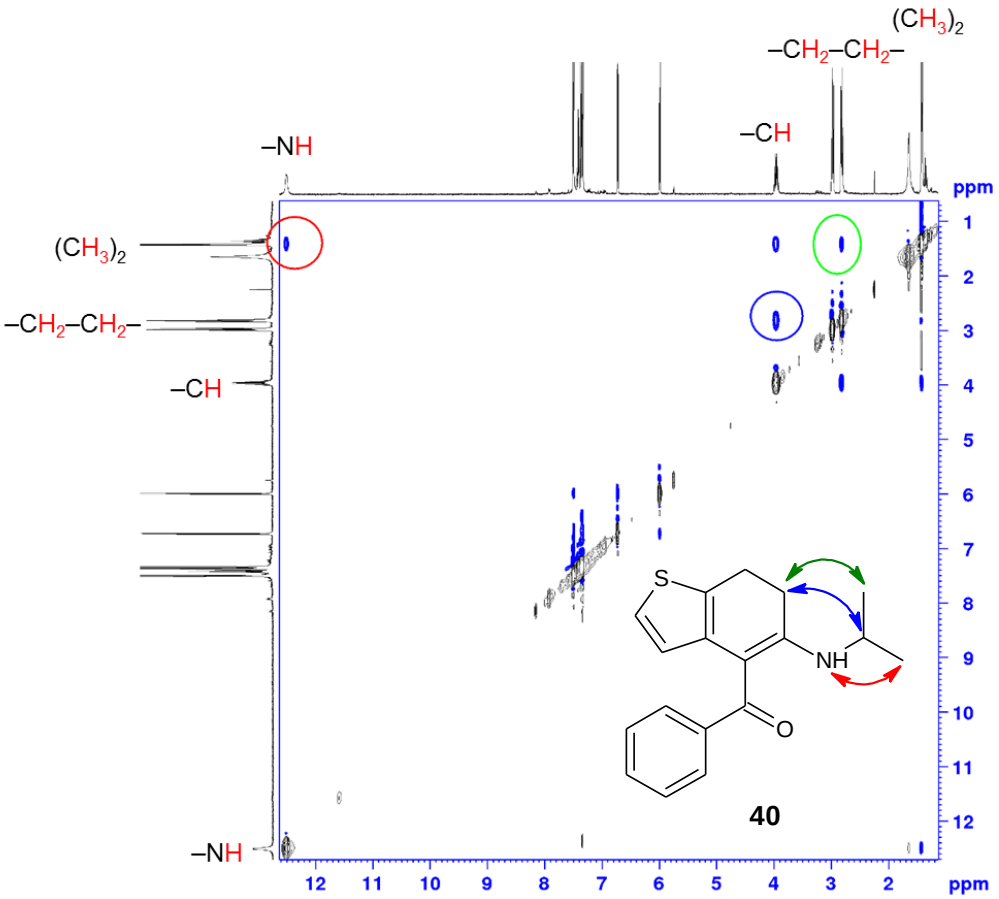
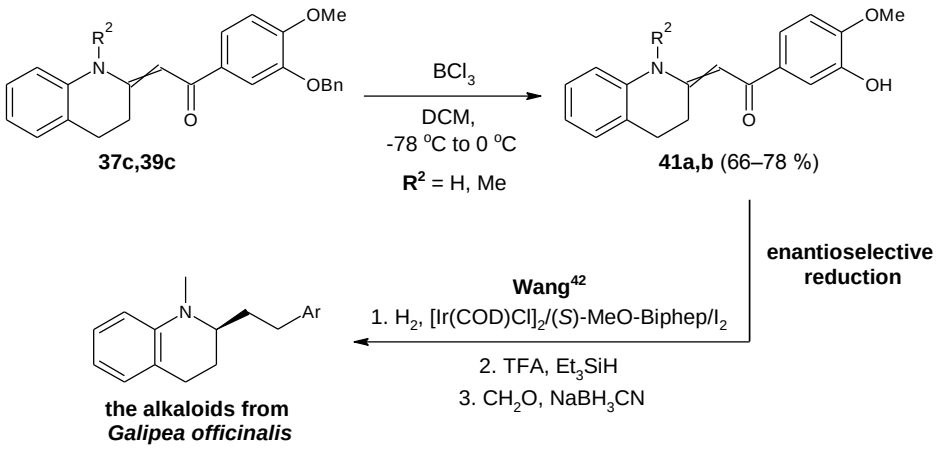


Figure 11 2D NOESY spectrum of **40** in $CDCl_3$ (400 MHz, mixing time 800 ms)

2.3 Preparation of the direct precursor for Galipeine

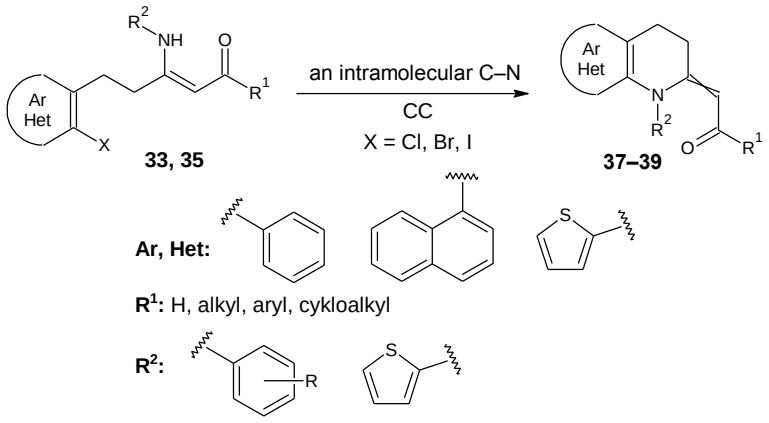
Debenzylation of hydroxy group in **37c, 39c** was accomplished using BCl_3 in DCM (Scheme 6). Compounds **41a, b** are the direct precursors for one *Galipea Officinalis* alkaloid galipeine. The approach using this kind of substrate for an enantioselective reduction was well-investigated and described by Wang et al.[42]



Scheme 6 Deprotection of **37c, 39c** and literature approach to the alkaloids

3 Conclusion

In conclusion, we have developed a new, simple, efficient and extended methodology leading to the various cyclic enaminones **37–39** (27 new tetrahydroquinolines **37, 39** and tetrahydrothienopyridines **38, 39** and one dihydrobenzothiophene **40**) using the transition metal catalyzed (Pd or Cu) intramolecular C–N CC of corresponding acyclic β-enaminones **33, 35** (Scheme 7).



Scheme 7 The main goal of the study

Key to the success of CC was the convenient choice of the catalyst (generated *in situ* vs well-defined precatalyst), ligand, base and solvent with respect to the structure of the starting enaminone **33, 35** (leaving group and substitution). These crucial factors were optimized and have been summarized and evaluated in the doctoral thesis. Screening of many types of catalytic systems revealed seven suitable protocols. The conditions included both the traditional catalytic systems and modern preformed precatalyst. Moreover, all prepared tetrahydropyridines **37–39** are cyclic enaminones with exocyclic double bond which can serve as reactants for further synthetic transformation. The scope of both an intramolecular C–N CC reaction and novel palladium precatalysts to new substrates was extended.

A few structures of acyclic enaminones **33, 35** were initially chosen so that some of the final products **37b, d, 39b, d, 41a,b** were the direct precursors of the alkaloids from *Galipea officinalis* (see chapter Objectives, Figure 2). Otherwise, these precursors **37b, d, 39b, d, 41a,b** are hardly accessible and this method is superior to the methods published so far.[42–44]

In total, more than 120 novel compounds were prepared and characterized by means of ^{1}H, ^{13}C NMR spectroscopy, HRMS MALDI, elemental analysis, melting points and eight structures were confirmed by X-ray diffraction.

4 References

(1) Tamao, K.; Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 1–10.

(2) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34* (23), 5497–5508.

(3) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chemie Int. Ed.* **2005**, *44* (29), 4442–4489.

(4) Reaction, M.-C. C.-C. Wiley-VCH, Weinheim 2004.

(5) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chemie Int. Ed.* **2012**, *51* (21), 5062–5085.

(6) Hartwig, J. F. *Nature* **2008**, *455* (7211), 314.

(7) Valente, C.; Pompeo, M.; Sayah, M.; Organ, M. G. *Org. Process Res. Dev.* **2014**, *18* (1), 180–190.

(8) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116* (19), 12564–12649.

(9) Rudenko, D. A.; Shurov, S. N.; Stepanyan, Y. G. *Chem. Heterocycl. Compd.* **2011**, *47* (6), 661.

(10) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Synthesis (Stuttg).* **2009**, *2009* (7), 1209–1219.

(11) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2* (8), 1109–1112.

(12) Liu, Y.; Yu, C.-Y.; Wang, M.-X. *Arkivoc* **2003**, *2*, 146–154.

(13) Melkonyan, F. S.; Karchava, A. V; Yurovskaya, M. A. *J. Org. Chem.* **2008**, *73* (11), 4275–4278.

(14) Melkonyan, F.; Topolyan, A.; Yurovskaya, M.; Karchava, A. *European J. Org. Chem.* **2008**, *2008* (35), 5952–5956.

(15) Melkonyan, F. S.; Topolyan, A. P.; Karchava, A. V; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2010**, *46* (9), 1158–1160.

(16) Mori, M.; Uozumi, Y.; Shibasaki, M. *Heterocycles* **1992**, *33* (2), 819–830.

(17) Uozumi, Y.; Mori, M.; Shibasaki, M. *J. Chem. Soc. Chem. Commun.* **1991**, No. 2, 81–83.

(18) Vaswani, R. G.; Albrecht, B. K.; Audia, J. E.; Côté, A.; Dakin, L. A.; Duplessis, M.; Gehling, V. S.; Harmange, J.-C.; Hewitt, M. C.; Leblanc, Y. *Org. Lett.* **2014**, *16* (16), 4114–4117.

(19) Wu, X.; Jiang, R.; Wu, B.; Su, X.; Xu, X.; Ji, S. *Adv. Synth. Catal.* **2009**, *351* (18), 3150–3156.

(20) Wu, X.; Xu, X.; Su, X.; Chen, G.; Zhang, Y.; Ji, S. *European J. Org. Chem.* **2009**, *2009* (29), 4963–4970.

(21) Broz, B.; Ruzickova, Z.; Simunek, P. *ARKIVOC* **2016**, No. 5, 118–141.

(22) Doušová, H.; Horák, R.; Růžičková, Z.; Šimůnek, P. *Beilstein J. Org. Chem.* **2015**, *11*, 884.

(23) Horák, R. Diplomová práce: Využití enaminonů pro tvorbu tetrahydrochinolinového skeletu, Univerzita Pardubice, 2013.

(24) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. *ACS Catal.* **2012**, *2* (6), 1147–1164.

(25) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64* (15), 5575–5580.

(26) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2* (1), 27–50.

(27) Surry, D. S.; Buchwald, S. L. *Angew. Chemie Int. Ed.* **2008**, *47* (34), 6338–6361.

(28) Bruneau, A.; Roche, M.; Alami, M.; Messaoudi, S. *ACS Catal.* **2015**, *5* (2), 1386–1396.

(29) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chemie Int. Ed.* **2012**, *51* (14), 3314–3332.

(30) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79* (9), 4161–4166.

(31) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4* (3), 916–920.

(32) DeAngelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. *J. Org. Chem.* **2015**, *80* (13), 6794–6813.

(33) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2* (1), 57–68.

(34) Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31* (22), 7753–7808.

(35) Su, M.; Buchwald, S. L. *Angew. Chemie Int. Ed.* **2012**, *51* (19), 4710–4713.

(36) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68* (7), 2861–2873.

(37) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7* (18), 3965–3968.

(38) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3* (26), 4295–4298.

(39) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. *Chem. Eur. J.* **2013**, *19* (49), 16760–16771.

(40) Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12* (3), 480–489.

(41) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10* (16), 3505–3508.

(42) Wang, X.-B.; Wang, D.-W.; Lu, S.-M.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2009**, *20* (9), 1040–1045.

(43) Greenhill, J. V; Loghmani-Khouzani, H.; Maitland, D. J. *Tetrahedron* **1988**, *44* (11), 3319–3326.

(44) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74* (7), 2780–2787.