Multicomponent Reactions

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One-Pot Three-Component Synthesis of Vicinal Diamines via In Situ Aminal Formation and Carboamination

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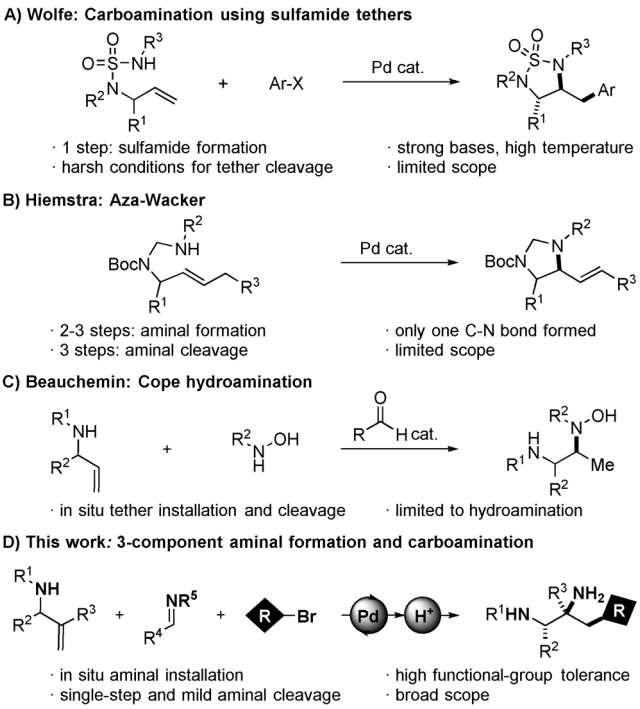
Abstract: *A synthesis of vicinal diamines via in situ aminal formation and carboamination of allyl amines is reported. Employing highly electron-poor trifluoromethyl aldimines in their stable hemiaminal form was key to enable both a fast and complete aminal formation as well as the palladium-catalyzed carboamination step. The conditions developed allow the introduction of a wide variety of alkynyl, vinyl, aryl, and hetereoaryl groups with complete regioselectivity and high diastereoselectivity. The reaction exhibits a high functional-group tolerance. Importantly, either nitrogen atom of the imidazolidine products can be selectively deprotected, while removal of the aminal tether can be achieved in a single step under mild conditions to reveal the free diamine. We expect that this work will promote the further use of mixed aminal tethers in organic synthesis.*

Vicinal diamines are of utmost importance in natural products, agrochemicals, drugs, and as chiral ligands.[1] Hence, tremendous efforts have been invested to develop new methods to access them efficiently.[2] Olefins have been widely used as simple and readily available substrates for the preparation of diamines.[3] The intermolecular diamination of alkenes through the formation of two new C–N bonds for example is one of the most-direct synthetic approaches.[2h,4] However, this strategy is often limited in scope and leads usually to identically substituted nitrogen atoms, thus hampering their differentiation and further elaboration. Tethering both nitrogen atoms to the olefin has been a successful approach to meet this challenge. The diamine motif is then accessed either via intramolecular diamination,[5] or through formation of one C–N bond when starting from allyl amine derivatives and forming a five-membered ring.[6] The latter might be accompanied by the simultaneous formation of another bond to the olefin. In particular, urea and sulfamide derivatives have been widely used in both approaches due to their robustness.[5,6] The use of palladium catalysis is particularly attractive, since it enables both the mono- and difunctionalization of olefins.[5a,c,6e–k] For example, Wolfe and co-workers described the use of classical sulfamide tethers for carboamination reactions (Scheme 1, **A**).[6h,i] However, the reaction requires strong *tert*-butoxide bases at elevated temperatures, and final cleavage of the sulfamide tether occurs in the presence of HBr at 130 °C for a prolonged period of time. Such harsh conditions are highly detrimental for the tolerance to functional groups and the scope of the reaction.



Scheme 1. Syntheses of diamines using a tether approach.

Therefore, we decided to focus on the use of aminals as C_{sp^3} tethers,[7] which have received much less attention than the classical urea and sulfamide tethers. They offer the precious advantage of being potentially more easily installed and removed, and could still engage efficiently in olefin functionalization processes. Furthermore, the obtained imidazolidine products provide a direct access to other highly important nitrogen-containing heterocycles such as imidazolines, imidazoles, and N-heterocyclic carbenes.[8] Among the groups who reported employing aminals as tethers, only two described the functionalization of nonactivated olefins (Scheme 1, **B** and **C**).[9] The seminal contribution of Hiemstra and co-workers describes the use of aminal tethers for Aza-Wacker cyclizations starting from allyl amines. However, tether installation and removal proved to be tedious, requiring five separate steps (Scheme 1, **B**).[9a] More recently, Beauchemin and co-workers reported a Cope-type hydroamination of simple allyl amines in one step (Scheme 1,

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C).[9b–f] While elegant, both works remain limited to a single C–N bond formation.

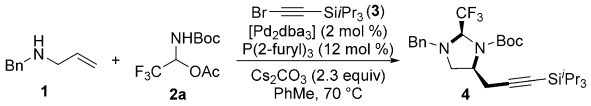
Recently, our group has demonstrated that vicinal amino alcohols could be synthesized from allyl amines using an acetal tether and a palladium catalyst to form simultaneously new C–O and C–C bonds.[10a] We envisioned that an allyl amine and an imine could in situ form an aminal, which would undergo a Pd-catalyzed carboamination reaction to generate an imidazolidine by formation of both a C–N and a C–C bond followed by hydrolysis to give the free diamine (Scheme 1, **D**).[11] All the reported mixed aminals employed for olefin functionalization bear electron-withdrawing groups on both nitrogen atoms, which greatly stabilize them. However, the poor nucleophilicity of the amine precursor prevents their fast synthesis.[7] We thought to use nucleophilic allyl amines to solve this issue. Three challenging conditions had to be met to ensure the success of the envisioned transformation:

1) formation of the aminal must be complete, fast, and selective to avoid side reactions or catalyst deactivation;
2) the mixed aminal formed needs to be both stable *and* suitable for the envisioned Pd-catalyzed carboamination;
3) the imidazolidine obtained must be stable under the reaction conditions to avoid catalyst poisoning, but still be amenable to a straightforward deprotection to free the diamine.

The efficient implementation of this approach is reported herein, employing electron-rich allyl amines, carbamate-protected trifluoroaldimines in their stable hemiaminal form, and a bromide, in the presence of a commercially available palladium source and phosphine ligands. The developed conditions allowed for a broad scope in both allyl amines and alkynyl, aryl, or vinyl bromides, as well as for high stereo-, regio-, and diastereoselectivity.

We started our studies with allylbenzylamine (**1**) and silyl acetylene **3** as efficient electrophilic partner in Pd^0/Pd^{II}-catalyzed olefin functionalization (Table 1).[10,12] We identified aldimine precursor **2a** as efficient tethering reagent in combination with $[Pd_2dba_3]$ as palladium source, P(2-furyl)$_3$ as ligand, and cesium carbonate as base. Under these conditions, imidazolidine **4** was isolated in excellent yield and diastereoselectivity (95%, d.r. > 20:1) (Table 1, entry 1). Importantly, **2a** is easily available on multigram scale,[13] bench stable for months, and only a slight excess is required to achieve complete conversion into **4**. As anticipated, the tether was of great importance for the reaction outcome. Electron-neutral aldimine **2b** was ineffective (entry 2), and even more-activated analogues still suffered from poor reactivity (entries 3 and 4). Various N-protected trifluoromethylaldimines or their precursors did provide some improvement, but furnished inferior results to **2a** (entries 5–9). Changing the ligand had also a profound effect. While using simple triphenylphosphine decreased the yield (entry 10), bulky PhDavePhos afforded **4** in high yield (entry 11). Electron-rich DavePhos was not efficient (entry 12). Regarding bidentate phosphines, BINAP was not competent, DPEPhos yielded 90% of **4**, and closely related XANTPhos only 58% (entries 13–15). Switching to cesium hydrogen carbonate as base reduced the yield significantly but still afforded a reasonable amount of **4**, while potassium carbonate provided 89% of the desired imidazolidine (entries 16 and 17). The use of such mild bases is very rare for Pd^0/Pd^{II}-catalyzed carboamination reactions, which often require stronger alkoxides. Deactivating the allyl amine with a carbamate protecting group led to very low conversion (entry 18). Finally, without palladium or ligand or base, **4** was not observed (entry 19).

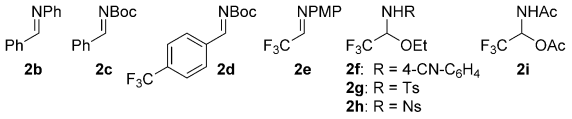
Table 1: Optimization of the tethered aminoalkynylation.[a]



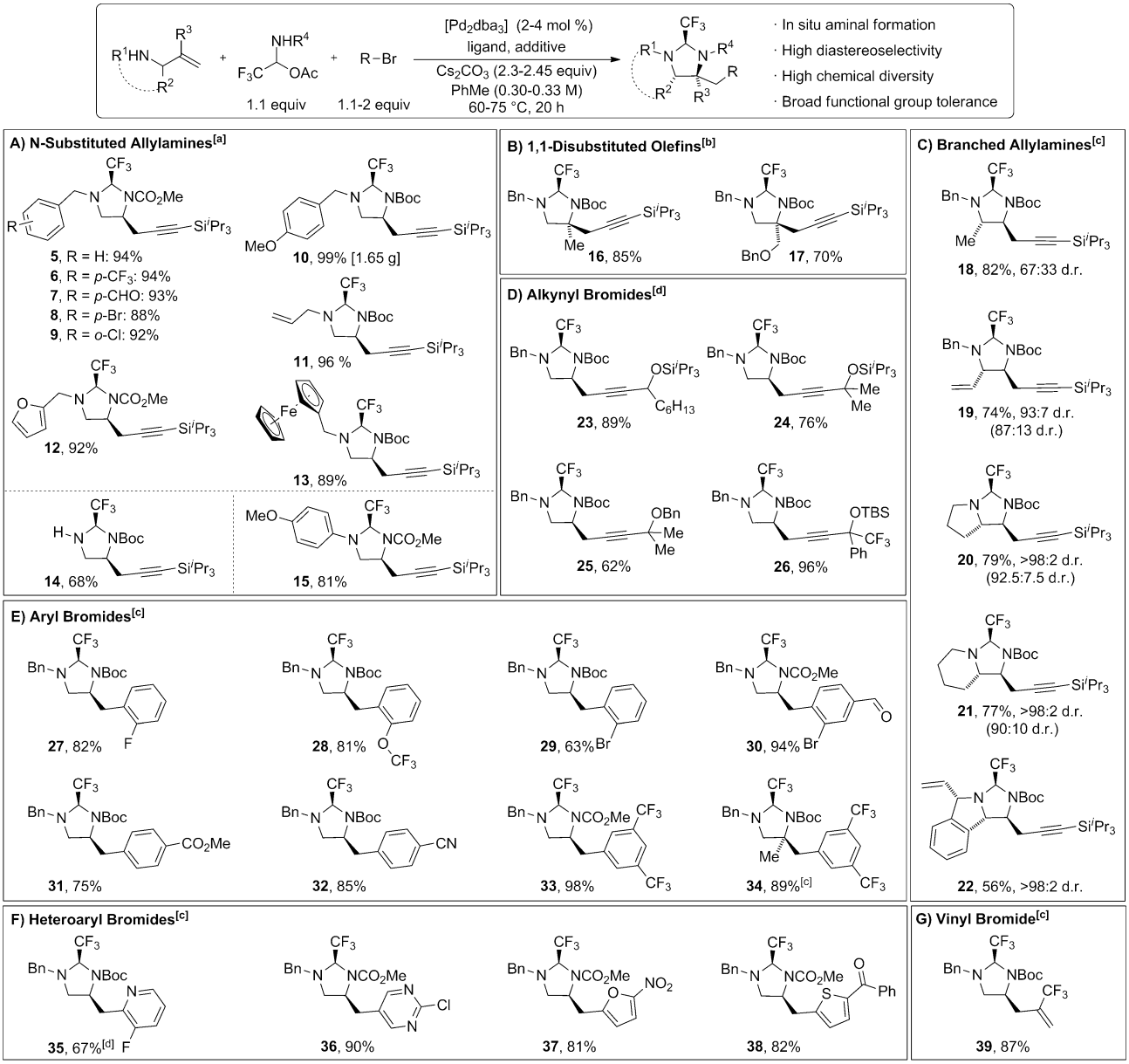
1 2a 4

Entry	Changes from standard conditions[b]	Yield [%][c]
1	none	99 (95)[d]
2	**2b** instead of **2a**	< 3
3	**2c** instead of **2a**	15
4	**2d** instead of **2a**	36
5	**2e** instead of **2a**	5
6	**2f** instead of **2a**	35
7	**2g** instead of **2a**	45
8	**2h** instead of **2a**	5
9	**2i** instead of **2a**	7
10	PPh_3 (12 mol%) instead of P(2-furyl)$_3$	39
11	PhDavePhos (11 mol%) instead of P(2-furyl)$_3$	81
12	DavePhos (11 mol%) instead of P(2-furyl)$_3$	11
13	BINAP (6 mol%) instead of P(2-furyl)$_3$	3
14	DPEPhos (6 mol%) instead of P(2-furyl)$_3$	90
15	XANTPhos (6 mol%) instead of P(2-furyl)$_3$	58
16	$CsHCO_3$ instead of Cs_2CO_3	44
17	K_2CO_3 instead of Cs_2CO_3	89
18	Benzyl allylcarbamate instead of **1**	8
19	without $[Pd_2dba_3]$ or P(2-furyl)$_3$ or base	< 3

[a] Reactions conditions: 0.10 mmol **1**, 0.11 mmol **2a**, 0.13 mmol **3**, 0.33 M in PhMe, 20 h. [b] DavePhos: 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; PhDavePhos: 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; BINAP: (1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine); DPEPhos: bis[(2-diphenylphosphino)phenyl] ether; XANTPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; PMP: *p*-methoxyphenyl. [c] Yield determined through NMR spectroscopy using 3,4,5-trichloropyridine as internal standard. [d] Yield of isolated product on 0.30 mmol scale.



The scope of the reaction was then examined (Scheme 2). We performed an assessment of functional-group tolerance and electronic effects by varying the substitution on the nitrogen atoms (Scheme 2, **A**). Use of a methyl carbamate protected tether provided product **5** in excellent yield. Modifying the benzyl group with electron-donating or -withdrawing groups had only minor influence (products **5**–**10**). Both the useful aryl bromide (product **8**) and chloride (product **9**) were preserved under these conditions. When the reaction was performed on gram-scale, compound **10** was obtained in quantitative yield. A simple allyl group was also tolerated, with no Heck side reaction observed (product **11**). Imidazolidines bearing a furan heterocycle or a ferrocene



Scheme 2. Scope of the tandem aminal-formation carboamination reaction. d.r. > 20:1 unless otherwise noted; d.r. in parenthesis represents the diastereoisomeric ratio in the crude reaction mixture if different from the one of the isolated compound. [a] $P(2\text{-furyl})_3$ (12 mol%) as ligand. [b] PhDavePhos (15–20 mol%) as ligand. [c] $P(2\text{-furyl})_3$ (24 mol%) as ligand and cesium triflate as additive (1.2 equiv). [d] DPEPhos (12 mol%) as ligand.

group were obtained in 92 and 89% yield, respectively (products **12** and **13**). The use of primary allyl amines was also possible (product **14**). Finally, replacing an aliphatic amine by an aniline still furnished the desired imidazolidine (**15**) in high yield.

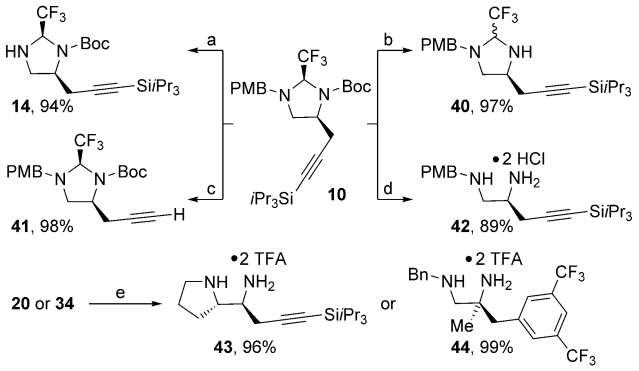
Geminal substitution of the olefin was possible when using PhDavePhos as ligand (Scheme 2, **B**). α-Tertiary amines **16** and **17** were formed in good to high yields and with high diastereoselectivity (d.r. > 20:1).

Next, we investigated α-substituted allyl amines (Scheme 2, **C**).[14] This class of substrates required the use of cesium triflate as additive to ensure high conversions.[15] Substitution by a methyl group furnished the desired imidazolidine **18** in high yield, albeit in low diastereoselectivity. A bis-allylic amine delivered product **19** in good yield and diastereoselectivity. Bicyclic and tricyclic imidazolidines **20, 21**, and **22** were formed in high diastereoselectivity. These results highlight the fast access to complex structures with control on up to four stereocenters in a single step.

Then, the scope of organohalides was examined. Alkynes derived from secondary and tertiary propargylic alcohols underwent the desired transformation in good to excellent yields (Scheme 2, **D**, products **23–26**). Notably, both aliphatic and aromatic substituents were tolerated at the propargylic position. We then turned our attention to aryl bromides (Schemes 2, **E**). This class of electrophiles could be used as

long as they were slightly activated with an electron-withdrawing group. While DPEPhos was a competent ligand in certain cases, the combination of $P(2\text{-furyl})_3$ with cesium triflate as additive was more general and reliable. *Ortho* and *para* substitution were well tolerated (products **27**–**32**). 1,2-Dibromoaryl derivatives underwent the reaction smoothly to afford brominated products **29** and **30**, which open up possibilities for further derivatization. Substitution at the *meta* positions cleanly delivered the desired products **33** and **34** bearing an α-secondary and an α-tertiary amine, respectively. Due to the importance of aromatic heterocycles in the agrochemical and pharmaceutical industries, several heteroaryl bromides were then submitted to the reaction conditions (Scheme 2, **F**). Gratifyingly, both fluoropyridine and chloropyrimidine were introduced in good to excellent yields (products **35** and **36**, respectively). Imidazolidines **37** and **38** bearing either a furan or a thiophene ring could be obtained in 81 and 82% yield, respectively. Finally, aminoalkenylation was also possible (Scheme 2, **G**). Trifluoromethyl-substituted olefin **39** could be isolated in 87% yield.

To highlight the synthetic potential of the obtained building blocks, we synthesized either of the free amines selectively (Scheme 3). Starting from **10**, oxidative cleavage of the PMB protecting group led to free amine **14** in high yield, while heating under microwave irradiation cleanly removed



Scheme 3. Orthogonal deprotection. Reaction conditions: a) DDQ, MeCN, H_2O, RT; b) microwave irradiation (160 °C), H_2O/Ethanol; c) TBAF, THF, 0 °C to RT; d) HCl, MeOH, −40 °C to RT; e) TFA, CH_2Cl_2, then MeOH, 0 °C to RT.

the Boc group to access **40** in nearly quantitative yield. Removal of $SiiPr_3$ with TBAF yielded terminal alkyne **41** in 98% yield. Finally, cleavage of the aminal was performed. Using HCl in methanol delivered diamine salt **42** in 89% yield. Treatment of imidazolidines **20** or **34** with trifluoroacetic acid (TFA) followed by addition of methanol allowed full removal of the tether in excellent yields, without any further purification. The mild acidic conditions used are routinely applied in peptide chemistry.

In conclusion, we have developed the first palladium-catalyzed carboamination of allyl amines employing an in situ installed C_{sp^3} aminal tether for the synthesis of 1,2-diamines. The use of carbamate-protected trifluoroaldimines in their stable hemiaminal form allowed excellent regio- and diastereoselectivities under mild reactions conditions, a high functional-group tolerance, and a broad scope. The versatility of our method was demonstrated by the introduction of alkynyl, aryl, heteroaryl, and vinyl groups into the allyl amines. Both free amines could be obtained orthogonally, while complete tether cleavage to give diamines was performed under mild conditions. Based on our results, we expect that the use of aminal tethers will find much broader application in the future.

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Keywords: alkenes · aminals · homogeneous catalysis · Pd catalysis · vicinal diamines

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Communications

Multicomponent Reactions

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One-Pot Three-Component Synthesis of Vicinal Diamines via In Situ Aminal Formation and Carboamination

Alkynyl, vinyl and aryl bromides
Wide substrate scope

up to 99% yield
up to d.r. > 98:2

Ideal combination: Vicinal diamines with a wide variety of alkynyl, vinyl, aryl, and hetereoaryl groups are obtained with complete regioselectivity and high diastereoselectivity via in situ aminal formation and Pd-catalyzed carboamination of allyl amines. Key to the reaction is the use of carbamate-protected trifluoromethyl aldimines in their stable hemiaminal form. Cleavage of the aminal tether was achieved under mild conditions.