Letter

Fully Automated Flow Protocol for C(sp³)−C(sp³) Bond Formation from Tertiary Amides and Alkyl Halides

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ABSTRACT: Herein, we present a novel C(sp³)−C(sp³) bond-forming protocol via the reductive coupling of abundant tertiary amides with organozinc reagents prepared *in situ* from their corresponding alkyl halides. Using a multistep fully automated flow protocol, this reaction could be used for both library synthesis and target molecule synthesis on the gram-scale starting from bench-stable reagents. Additionally, excellent chemoselectivity and functional group tolerance make it ideal for late-stage diversification of druglike molecules.

· Fully automated library synthesis
· 41 products, up to 91% yield
· Up to 4 reactions/h
· Scalable up to 0.8 g/h
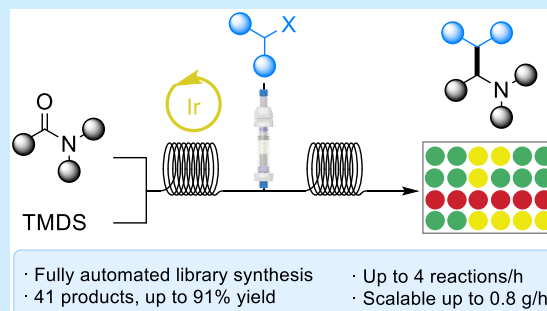
Robust and broad scope methodologies for C(sp³)−C(sp³) bond formation are of great importance in both medicinal and synthetic chemistry for providing predictable and rapid access to novel chemical space in an efficient manner.[1] Commonly, C(sp³)−C(sp³) bond formation is achieved via Ni-,[2] Pd-,[3] Co-,[4] and Fe[5]-catalyzed cross-coupling from halogenated precursors, acid derivatives, or by addition of nucleophiles and radicals to activated systems, i.e., Giese and Reformatsky-type reactions.[6] However, performing such transformations in a high-throughput format remains a challenge and currently places limitations on its applicability in drug discovery.[7] As part of an ongoing program to address this, recently our group reported an automated flow photochemistry platform to perform Giese-type radical additions on activated alkenes using a halogen atom transfer (XAT) approach to enable C(sp³)−C(sp³) bond formation.[8]

The amide functional group is undoubtedly the most ubiquitous pharmacophore in bioactive natural molecules (i.e., peptides) and drug compounds. From a chemical reactivity point of view, the amide is stable and can be considered as mostly inert toward the majority of reagents and, until recently, was rarely employed as a substrate for C(sp³)−C(sp³) bond formation.[9] By making this abundant functional group a suitable reactive intermediate for downstream diversification, the possibility to re-explore many druglike compounds in a strategically new way would be enabled. Indeed, recent reports from the groups of Nagashima,[10] Huang,[11] Chida and Sato,[12] and Dixon,[13] among others,[14] have demonstrated that tertiary amides can act effectively as iminium ion and enamine precursors.[15] Carbon-centered nucleophilic trapping reagents for in situ generated iminium ions have so far ranged from cyanide[13c] and acetylide[11a] through to Grignard reagents.[13d]

Furthermore, functionalized difluoromethyl groups could also be introduced via appropriate difluoroacetate ester and amide Reformatsky reagents.[13f] Despite these advances, the scope of the current amide reductive functionalization methodologies is limited by the narrow set of nucleophiles used.
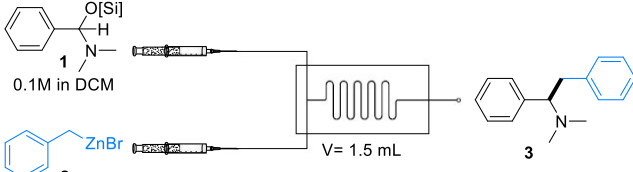
We recognized that broadening the transformation to a larger set of organometallic nucleophiles would expand its applicability and value-adding relevance, particularly for library synthesis. This would be especially true if the coupling reactions were performed in an automated manner, and in this case, a flow setup could be envisioned as the most suitable platform to run such chemistry in a machine-assisted way. Both reagents, the hemiaminal intermediate [obtained by partial amide reduction with Vaska's complex and tetramethyldisiloxane (TMDS)] and the organometallic reagents, are unstable/reactive by their nature, and flow would permit both chemicals to be prepared and reacted in-line with a suitable computer-controlled process.

The in-line coupling of the silylated hemiaminal **1** derived from *N,N*-dimethylbenzamide with benzylzinc bromide was chosen as a model reaction (Table 1). Optimization was achieved quickly by building on our previous experience regarding reactions of hemiaminals and organozinc reagents[16] and our recent protocol.[13f]

Table 1. Optimization of the Organozinc Addition Step

entry	equiv of **2**	t_R (min)	yield (%)[a]
1	2	1	87
2	2	3	86
3	2	5	92
4	3	5	95
5	1.4	5	52
6	2.2	5	95

[a]Yield determined by ^{1}H NMR against 1,3,5-trimethoxybenzene as internal standard.

We performed the reaction in a chip reactor at room temperature to determine time and equivalents required for the organozinc coupling step (Table 1). The silylated hemiaminal **1** was prepared in batch in CH_2Cl_2 following our protocol,[13c] and benzylzinc bromide **2** was prepared by flowing a solution of benzyl bromide in THF through a column filled with zinc powder, as reported by our group.[17] The initial attempt with 2 equiv of **2** with a t_R of 1 min very pleasingly provided the desired product **3** in good yield (87%, entry 1). Increasing the residence time to 5 min improved the yield up to 92% (entry 3). Increasing the equivalents of organozinc reagents provided a slight increase in yield (entry 4), but decreasing the equivalents resulted in a clear drop in conversion to product (entry 5) as the excess of silane also reacted with the organometallic reagent. The best balance was found using 2.2 equiv of organozinc **2** with a residence time of 5 min (entry 6), which represented an improvement over the previous procedure in terms of equivalents and time.[13f]

The scope of the flow protocol was assessed using 2.2 equiv of organozinc reagent and a 0.1 M solution of silylated hemiaminal freshly prepared following conditions described in the literature (Figure 1).[13c] The desired amine products were obtained in moderate to excellent yields, and the reaction additionally showed a high functional group tolerance by being compatible with halogens, esters, nitriles, carbamates, and lactams. For benzyl zinc analogues, it was observed that substituents at the *o*-, *m*-, and *p*-positions were tolerated (compounds **4**−**15**), although lower yields were observed with *ortho* substituents presumably because of steric effects (**12** and **13**). Importantly, the in-line coupling reaction also worked with other primary, secondary, and tertiary organozinc reagents to provide the desired products (**16**−**24**) in moderate to good yields. From this group of reagents, it is important to highlight the formation of quaternary carbon centers in compounds **21**−**24**, which still remains as a challenging transformation in modern synthetic chemistry.[1b] Moreover, the reaction allowed the introduction of other functionalized alkyl groups, such as tetrahydropyran **18** and *N*-Boc-protected piperidine **19**. Both of these structural motifs are of high importance for medicinal chemists and are not easily accessible by other procedures. In agreement with previous reports, other benzamide analogues were also successfully employed in the reaction (**25**−**30**). After exploring the preliminary scope for the C(sp³)−C(sp³) bond formation, we focused our attention on expanding the scope of amides
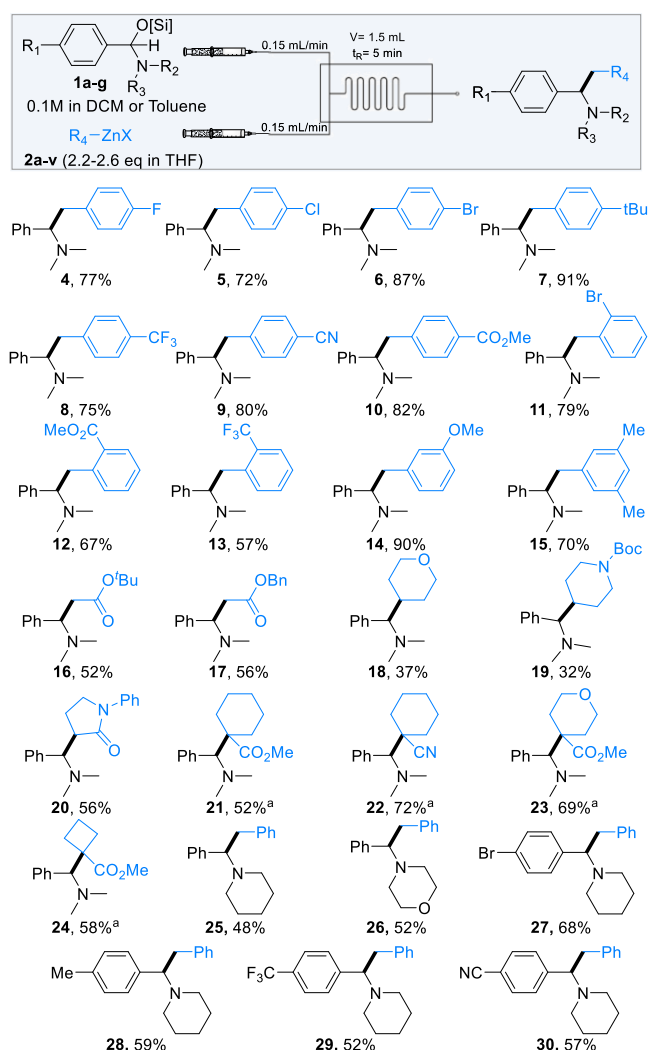

Figure 1. Scope of organozinc and benzamide reagents. [a]2.6 equiv of organozinc reagent were used, and hemiaminal was formed in toluene.

suitable for this reaction, especially lactams that are of importance to medicinal chemistry.[18] As the silyl hemiaminals from lactams are typically less stable than those from benzamides, we also explored the Vaska's complex-catalyzed reduction step in flow to determine the time and equivalents of TMDS required for its reduction.[13] *N*-Phenylpiperidone **31** was selected for this study. Two solutions, one with the reducing agent in toluene and the other with the lactam and the Vaska catalyst, were mixed and allowed to react; then, this solution was collected over $CDCl_3$ under nitrogen atmosphere, and the ^{1}H NMR was measured directly after collection to evaluate the conversion (see Supporting Information). Repeating this experiment at different residence times allowed us to determine that the lactam was fully reduced in only 5 min (see Supporting Information). Then, using 5 min as the fixed residence time in the reactor, the experiment was repeated at different concentrations of TMDS to determine the equivalents required for the reduction step. Finally, 1.7 equiv of TMDS and 5 min of residence time proved to be the ideal conditions to combine this step with the subsequent coupling reaction. This experiment was performed in a three-inlet system using the two solutions described above and a third one containing organozinc **A** in THF. To allow further automation, a Vaportec RS-400 flow instrument was used (see Supporting Information). The system

allowed the automated injection of the different solutions in their corresponding loops before performing the reaction in the reactor area (Figure 2i). The combination of a 5 mL reactor for the first step and the 10 mL reactor for the second allowed to get 5 min residence time in both reactions, thereby mimicking the optimized conditions observed for each step. In this way, compound **31A** was obtained in 67% isolated yield. Taking advantage of the automated setup, we chose to perform a heatmap combining six different lactams with four different

organozinc reagents to explore the potential of the approach for library synthesis. Amides **31** to **36** were selected to cover ring sizes from five to seven atoms, alkyl, aryl and heteroaryl substitution at the nitrogen, and fused systems. As organozinc reagents, **A** to **D** were selected to cover different reactivities and substitution patterns. All solutions were loaded into the autosampler, and all combinations were run in an unattended manner at a rate of 4 compounds per hour. Reactions were collected, and conversion was analyzed by LC-MS to provide the corresponding heatmap (Figure 2ii). Results showed that all combinations produced the desired compounds in reasonable yield except when the organozinc derived from azetidine **C** was used where product was not detected, probably because of its lower nucleophilicity. Compounds **32A**, **33A**, **34A**, **33B**, **35B**, **36B**, **31D**, **32D**, **33D**, and **35D** were successfully purified by automated mass-triggered preparative HPLC in suitable amounts for biological evaluation.[19] Taken as a whole, this study clearly supports the automated flow approach for library synthesis.

To complete the validation of the heatmap, compounds **33A**, **34A**, and **36A** were scaled up to corroborate the conversion observed with different conversion data, which varied from middle range to the high range and at different scales (5 to 20 times larger than library scale). For the scale up experiment we chose to start from all commercially available reagents and prepare the organozinc derivative with the zinc column, also in-line (see Supporting Information). In all cases the observed reaction conversions were higher than the one at 0.2 mmol scale because of the broader steady state that can be achieved at larger scale. Isolated yields were all aligned with the observed conversion. In terms of productivity, compounds were obtained up to a rate of 0.8 g/h. These results proved that the chemistry could be performed all in-line so that by starting from an amide and an alkyl halide the reductively coupled product could be obtained in only 10 min of total residence time.

Finally, validation of the reaction was done with druglike compounds and key intermediates. For these experiments, the telescoped setup was used to access products from warehouse reagents in a more efficient way. Lactam **37**, prepared from an intermediate described in patent literature for compounds with mGluR5 PAM activity, was selected as a druglike compound.[20] Lactam **39** was selected as a valuable intermediate example because boron analogues are important building blocks for drug discovery and have not been previously reported with this chemistry (Scheme 1). Both compounds **38** and **40** were isolated in useful yields without modifying the standard protocol. Additionally, a last experiment was run using diethyl zinc as the nucleophile to expand the scope to dialkylzinc analogues. Compound **41** was obtained in similar yield from intermediate **37**, thereby demonstrating that other nucleophiles can be used without modifying the reaction conditions.

In summary, we have developed a new protocol to form $C(sp^3)-C(sp^3)$ bonds by reductive activation of tertiary amides followed by nucleophilic attack of organozinc reagents. Because of its impressive functional group tolerance, this flow protocol allowed the introduction of a diverse set of functionalized alkyl groups, thereby generating interesting and relevant intermediates that can be used as building blocks for organic synthesis and medicinal chemistry. We have also demonstrated that the protocol can be fully automated and made suitable for library synthesis at a rate of four reactions per hour. Because all steps are performed in flow, the procedure is scalable at gram/hour productivity starting from bench-stable reagents. We have also
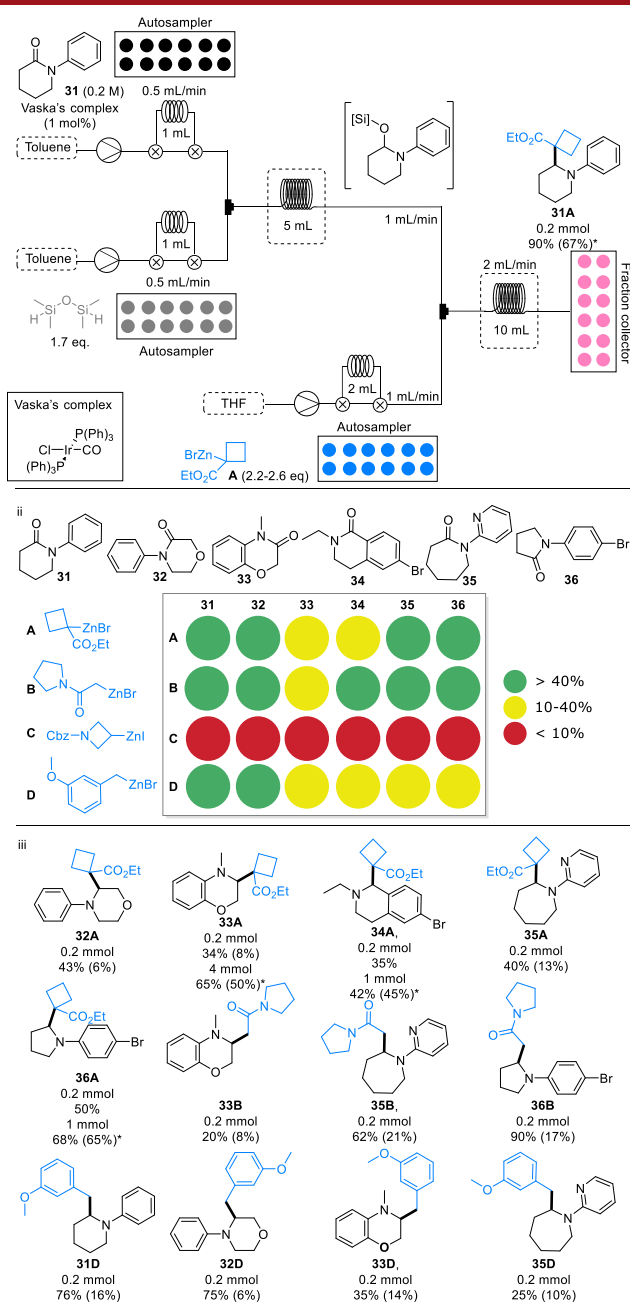

Figure 2. Automated synthesis approach. (i) Set up of the automated flow system. (ii) Heatmap obtained after combining lactams **31**−**36** with organozinc **A**−**D**, conversion was analyzed by LC/MS. (iii) Isolated compounds from the heatmap and LC/MS conversion (isolated). At 0.2 mmol scale, compounds were purified by automated preparative liquid chromatography coupled with MS detection (isolated amount in brackets); at 1 and 4 mmol scale compounds were purified by column chromatography (isolated yield in brackets).

Scheme 1. Application to Druglike Compounds and Key Intermediates
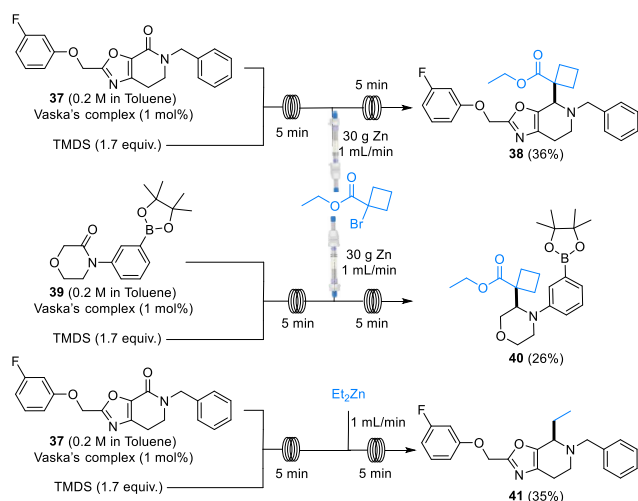
demonstrated that this chemistry can be used for late-stage derivatization of druglike compounds, thereby opening new avenues for drug discovery. Applications of this methodology in medicinal chemistry programs will be a subject of our future studies.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

ⓢⓘ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01390.

General procedures, compound characterization, and NMR spectra for batch flow and automated flow (PDF)

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Notes

The authors declare no competing financial interest.

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