Green Chemistry

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DOI: 10.1039/C7GC02643A

Journal Name

COMMUNICATION

Diphenylsilane as a Coupling Reagent for Amide Bond Formation

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A simple procedure for amide bond formation using diphenylsilane as a coupling reagent is described. This methodology enables the direct coupling of carboxylic acids with primary and secondary amines, releasing only hydrogen and a siloxane as by-products. Only one equivalent of each partner is needed, providing a more sustainable amidation method producing minimal wastes. This methodology was also extended to the synthesis of peptides and lactams by addition of Hünig's base (DIPEA) and 4-dimethylaminopyridine (DMAP).

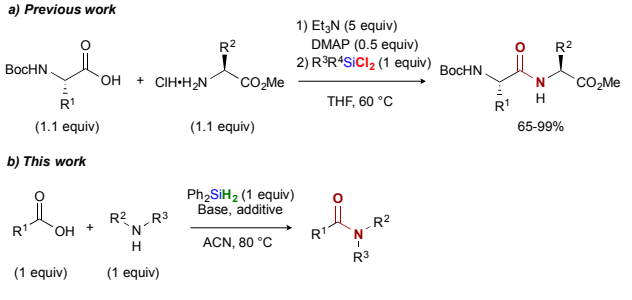
Amide bonds are prevalent in nature as the backbone of proteins and are also found in high-added-value products, such as pharmaceuticals and polymers, due to the high bond polarity and stability. Indeed, amide bond formation is the most commonly used reaction for the synthesis of pharmaceuticals, accounting for 16% of all reactions; the amide bond can be found in 25% of pharmaceuticals currently on the market.[1] Traditional methods to form amide bonds require preactivation of the carboxylic acid moiety and the use of stoichiometric coupling reagents with additives.[2] These methods are general; however, some drawbacks include poor atom economy, high cost and reagents or by-products that are both toxic and hazardous.[3] Consequently, amide bond formation has been recognized as one of the most important reactions used in industry requiring more efficient and sustainable procedures.[4]

Over the last decades, many alternatives have been developed,[5] such as the use of carboxylic acid surrogates (thioacids,[6a,b] esters,[6c,d] alcohols,[6e,f] functionalized aldehydes,[6g,h] ketones,[6i,j] α-keto acids,[6k] potassium acyltrifluoroborates (KATs),[6l] nitriles,[6m,n] alkynes[6o,p]), α-bromo nitroalkanes[7] with amines, or the use of amine surrogates (isocyanates,[8a,b] isonitriles,[8c] azides,[8d] sulfonamides,[8e,f] CDI-activated α-aminoesters[8g]) with carboxylic acids. Although efficient and elegant, these methods require prefunctionalization of one of the coupling partners or the use of an alternative functional group to carboxylic acids or amines. An interesting strategy is the direct amide formation from carboxylic acids and amines, which can be achieved by using organoboron derivatives,[9] a zirconium catalyst[10] or fluorouronium reagents.[11] However, methods using boronic acids, for instance, generally require harsh conditions (high temperature).

We have already developed a direct amidation procedure using 9-silafluorenyl dichlorides as coupling reagents.[12] A similar strategy was first reported in 1969 by Chan, who described silicon tetrachloride as an efficient coupling reagent for amide bond formation.[13] Furthermore, Liskamp reported the use of dichlorodialkyl silanes for the synthesis of amides by a protection-activation strategy.[14] Our previously developed method enables the synthesis of a range of dipeptides in excellent yields with minimal epimerization. However, 9-silafluorenyl dichlorides are not commercially available and are moisture-sensitive reagents (glovebox storage necessary). Furthermore, significant quantities of base are needed to neutralize the HCl formed during the reaction.

Herein we describe the use of commercially available and stable diphenylsilane as coupling reagent for direct amide bond formation (Scheme 1).

Scheme 1 Amide Bond Formation by Si-Ligation.



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Electronic Supplementary Information (ESI) available: experimental procedures and characterization data (PDF). See DOI: 10.1039/x0xx00000x

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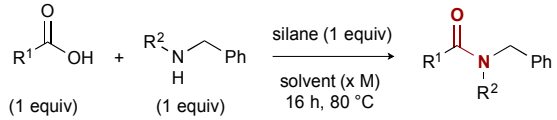
DOI: 10.1039/C7GC02643A

Phenylsilane has already been reported as a coupling reagent for amide synthesis.[15] However, 10 equivalents of the amine partner and 20 equivalents of phenylsilane were needed, and no mechanism was proposed. In the present method, preactivation of either partner is not required and, in the case of simple amides, additional additives are not needed. This simple and atom-economical procedure releases only dihydrogen and a siloxane as by-products, enabling the formation of amide bonds in a more sustainable manner with minimal waste.

Dihydrosilanes are commonly used as reducing agents, generally with metals.[16] Notably, they have been used for alkylation and formylation of amines with carboxylic acids or carbon dioxide.[17] In an alkylation reaction using methylphenylsilane as a hydride source, Minakawa reported that "no amide side products were observed" under the reported conditions.[17b] However, Beller observed phenylacetamide formation while optimizing a direct *N*-alkylation of amines with carboxylic acids with Karstedt's catalyst.[17c]

As ruthenium complexes are often used to activate Si–H bonds,[17b,18] we first attempted to couple acetic acid with benzylamine in presence of $[RuCl_2(p\text{-cymene})]_2$ catalyst and diphenylsilane without solvent (Table 1, entry 1). Significant H_2 release was observed, and the product was obtained in excellent yield in a really clean manner. While performing control experiments, we were pleased to observe that no catalyst was needed (entry 2). As most carboxylic acids are solids, we chose phenylacetic acid as coupling partner for the optimization. Based on our previously developed method with dichlorosilanes, tetrahydrofuran (THF) was first employed, affording the desired product in moderate yield (entry 3). The use of acetonitrile to solubilize starting materials enabled amide bond formation in excellent yield (entry 4). However, when these conditions were applied to a secondary amine, the product was obtained in a low yield (entry 5).

Table 1 Optimization of amide formation



Entry	R^1	R^2	Silane	Solvent	[C] (M)	Yield (%)[a]
1[b]	Me	Me	Ph_2SiH_2	-	-	94
2	Me	Me	Ph_2SiH_2	-	-	98
3	Bn	H	Ph_2SiH_2	THF	0.5	61
4	Bn	H	Ph_2SiH_2	MeCN	0.5	86
5	Bn	Me	Ph_2SiH_2	MeCN	0.5	36
6	Bn	Me	Ph_2SiH_2	MeCN	2.5	78
7	Bn	H	Ph_2SiH_2	MeCN	2.5	90
8	Bn	H	$PhSiH_3$	MeCN	0.5	81
9	Bn	H	Me_2PhSiH	MeCN	0.5	32
10	Bn	H	Ph_3SiH	MeCN	0.5	50
11	Bn	H	Et_2SiH_2	MeCN	0.5	14
12	Bn	H	$MePhSiH_2$	MeCN	0.5	76

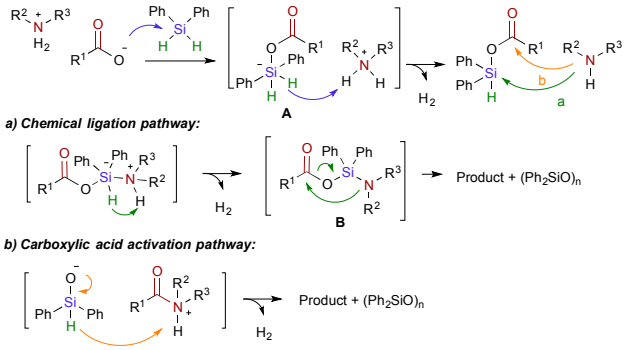
[a] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] $[RuCl_2(p\text{-cymene})]_2$ used as catalyst (1 mol %).

Notably, using a higher concentration (2.5 M) afforded the desired amide in good yield (entry 6). A high concentration is ideal for greener procedures.

To gain mechanistic insights, we studied different silanes: monohydrosilanes, dihydrosilanes and phenylsilane (entries 8–12). Phenylsilane gave a similar yield to the one obtained with diphenylsilane (entry 4 *vs* 8). As with our previously developed method using dichlorosilanes, we postulate a chemical ligation pathway whereby a silicon intermediate linked to both partners can rearrange upon heating to form the amide bond (Scheme 2a). However, amide formation was also observed with monohydrosilanes, albeit in much lower yields (entries 9–10). Therefore, it is probable that the reaction can also proceed *via* a competitive pathway involving simple activation of the carboxylic acid followed by nucleophilic attack by the amine, leading to the same final product (Scheme 2b). Upon nucleophilic attack of the carboxylate, a pentacoordinate silicon intermediate **A** can be formed, thus weakening the Si–H bond that can act as a hydride donor.[19] Despite our efforts, we were unable to observe the putative intermediate **B**. However, a series of control experiments showed that diphenylsilane reacts with both partners independently, supporting its formation.[20] In a recent publication, Denton described a similar intermediate in a mechanistic study of catalytic Staudinger amidation.[21] Next, we investigated the influence of varying the silicon substituents (entries 11–12). When triethylsilane was used, we observed a dramatic decrease in yield from 86% to 14% (entry 11 *vs* 4). Indeed, aromatic groups are required to stabilize intermediate **A**. Exchanging an alkyl group for an aromatic group provided an improved yield (entry 12).

Next, we explored the scope of the reaction. First, neat acetylations of different amines were performed in good to excellent yields (Scheme 3, **1a-d**). Then, several amides were synthesized with the developed method in good yields. Various acids including benzylic (**1e**), aromatic (**1f**) and aliphatics (**1g-h**) can be used with good to excellent yields. SFC traces showed minimal epimerization (3%) for the stereocenter containing acid (**1g**). Alkenes and alkynes are tolerated (**1i-j**), as well as a furan ring (**1k**). Tertiary amides can also be obtained in good to excellent yields from disubstituted or cyclic amines (**1l–n**). Unfortunately, when using benzoic acid, a lower yield is observed (**1q**).

Scheme 2 Postulated mechanism



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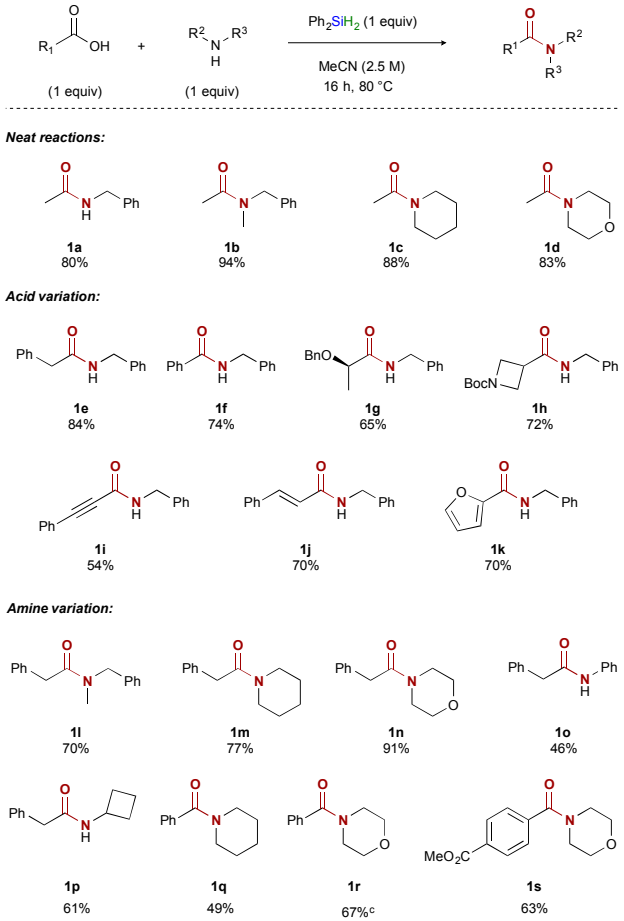
Scheme 3 Amide formation.[a,b]



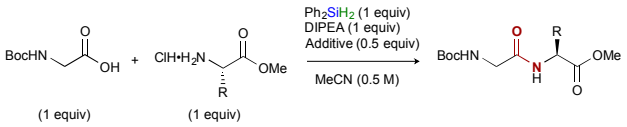
[a] Reaction run on a 0.5-mmol scale. [b] Isolated yield. [c] 42-h reaction time.

However, a longer reaction time (**1r**) or the use of an electron-withdrawing group (**1s**) gave better yields. Next, we focused on the more challenging peptide coupling reaction.

We began our studies with the simplest coupling between Boc–Gly–OH and NH_2–Gly–OMe•HCl (Table 2). Unfortunately, no product was obtained using our previous conditions (entry 1). After a quick optimization, we demonstrated that the dipeptide could be obtained in excellent yield (entry 3) by adding Hünig's base and DMAP. However, when the more hindered NH_2–(*L*)Phe–OMe•HCl was used, the yield dropped significantly (entry 5). Increasing temperature to 80 °C and reaction time to 42 h was beneficial to the reaction (entries 6–8) and afforded the desired dipeptide in 90% yield (entry 8).[22] Microwave heating was unsuccessfully employed to reduce reaction time. Gratifyingly, DMAP, an expensive reagent, could be replaced by pyridine with no modification in yield (entry 9). Nevertheless, pyridine cannot be used as base due to its lower pKa (entry 10).

With these new conditions in hand, dipeptide formation was investigated (Scheme 4). When Boc–Gly–OH was used as the carboxylic acid partner, good to excellent yields were obtained (**2a–c**). Moreover, the reaction can be scaled up to 2 mmol without any decrease in yield (**2b**).

Table 2 Optimization of conditions for peptide coupling reaction



Entry	R	Base	Additive	Time (h)	T (° C)	Yield (%)[a]
1	H	-	-	16	60	0
2	H	DIPEA	-	16	60	68
3	H	DIPEA	DMAP	16	60	99
4	H	Et_3N	DMAP	16	60	78
5	Bn	DIPEA	DMAP	16	60	42
6	Bn	DIPEA	DMAP	16	80	66
7	Bn	DIPEA	DMAP	16	100	58
8[b]	Bn	DIPEA	DMAP	42	80	91
9	Bn	DIPEA	Pyridine	42	80	90
10[c]	Bn	-	Pyridine	42	80	39

[a] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Reaction run on a 2-mmol scale. [c] 1.5 equiv of pyridine used.

However, employing more hindered carboxylic acids was more challenging: using Boc–(*L*)Ala–OH, Boc–(*L*)Phe–OH or Boc–(*L*)PheGly–OH decreased reactivity. Still, corresponding dipeptides were obtained in moderate yields (**2d–f**).

Finally, we wanted to apply our method to tripeptide synthesis. After a simple deprotection at both ends independently, Boc–Gly–(*L*)Phe–OMe was coupled to NH_2–Gly–OMe•HCl (for the Boc deprotected residue) and to Boc–Gly–OH (for the ester hydrolyzed residue) (**2g–h**). C to N synthesis (**2g**) as well as N to C synthesis (**2h**) gave a moderate 50% yield. For the C to N synthesized tripeptide **2g**, this low yield can be attributed to steric hindrance from the carboxylic acid residue as observed previously. In the case of N to C synthesis, considering the steric hindrance of both partners, tripeptide **2h** should have been obtained in higher yield. This moderate yield can be attributed to product inhibition that we observed during our studies.[23] It should be pointed out that these conditions led to significant product epimerization when *N*–Boc–phenylglycine was used as the coupling partner (see Electronic Supplementary Information). However, only one diastereoisomer was observed for **2d**. This methodology also provided small lactams in good yields (**3a–c**).

Scheme 4 Peptide and lactam synthesis.[a,b]

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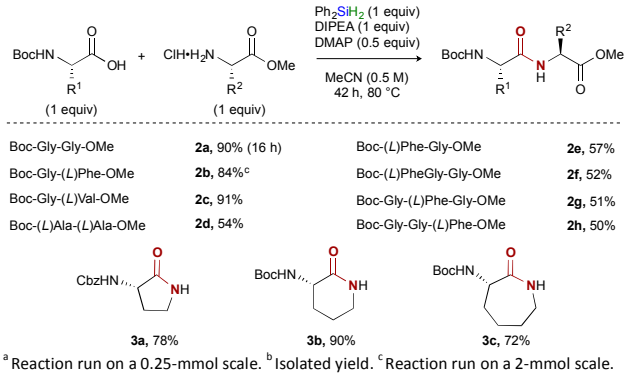

[a] Reaction run on a 0.25-mmol scale. [b] Isolated yield. [c] Reaction run on a 2-mmol scale.

Notably, this method is compatible with both Boc and Cbz protecting groups. However, the Fmoc protecting group was cleaved under reaction conditions.

Conclusions

In summary, we have developed a simple and more sustainable amidation procedure. Despite long reaction times, this methodology offers an atom-economical and environmentally attractive way to form amide bonds compared to traditional methods. Commercially available unactivated carboxylic acids and amines can be coupled in good yields using one equivalent of inexpensive and stable diphenylsilane. The only by-products of this reaction are H_2 and a siloxane that can be filtered off, providing a clean crude product that can be easily purified by a rapid flash column chromatography. This study provides a proof of concept that dihydrosilanes can be used without any metals to form amide bonds through a putative chemical ligation pathway. Moreover, this methodology can be applied to dipeptide and lactam synthesis by adding Hünig's base and DMAP or pyridine.

We gratefully thank the Natural Science and Engineering Research Council of Canada (NSERC) Discovery Grant RGPIN-06438, the Canada Foundation for Innovation Leaders Opportunity Funds 227346, the Canada Research Chair Program CRC-227346, the FRQNT Centre in Green Chemistry and Catalysis (CGCC) Strategic Cluster RS-171310, and Université de Montréal. M. S. is grateful to Université de Montréal for postgraduate scholarship.

Conflicts of interest

There are no conflicts to declare.

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20 See ESI for control experiments.

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22 Free amine can also be used instead of HCl salt, giving similar yields (80% yield without DIPEA and 87% yield with DIPEA).

23 When 1 equivalent of Boc–Gly–Gly–OMe was added at the beginning of reaction, for the coupling of Boc-Gly-OH with NH_2-(*L*)Phe-OMe•HCl, the desired dipeptide was obtained in only 52% yield compared to the 91% yield obtained in standard conditions.

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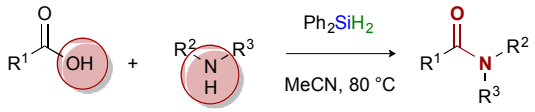

- *Metal-free procedure*
- *Commercially available coupling partner*
- *H_2 and a siloxane as by-products*

A simple amidation procedure enabling the direct coupling of carboxylic acids to amines using one equivalent of diphenysilane is reported.