A Bee-line Approach to Access Organocatalysts: A Suitable Base Catalyzed, Time-dependent, Chemoselective O-functionalization of Prolinol

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This paper is dedicated to Prof. Petri M. Pihko on his 51st birthday

Abstract: Herein a successful chemoselective either functionalization of the nucleophilic sites of prolinol by exploiting the relative acidity difference and inverted nucleophilicity of the corresponding conjugate bases, employing a suitable base is reported. An elaborate investigation into the overlooked sensitivity of reaction conditions to a highly utilized protocol has been reported. As an example, mono-Boc functionalization of prolinol for the exclusive synthesis of either NBoc/OBoc/Oxazolidinone derivatives is reported. Failing to emulate the former protocols, a mechanistic investigation was initiated which revealed that the rudimentary steps can be controlled by: *a)* a requisite base to recognize the differently acidic sites (NH and OH) for the formation of the conjugate base reacting to the electrophile, *b)* the disparity in nucleophilicity of the completely formed conjugate basic sites. This protocol has been extended to be successful with various other substrates, which might prove to be applicable as suitable catalysts in asymmetric reactions. Never-reported-before substrates such as O-Boc, O-CBz, O-Bz and O-ethyl carbonate derivatives of prolinol were synthesized in good to excellent yields along with other substrates.

Introduction

Proline as a starting material has enormous use in synthetic organic chemistry as well as biochemistry.[1] Seminal work done by List in the year 2000 with subsequent explorations has proved proline as an excellent alternative to biocatalysts.[2] Proline is a simple yet archetypical catalyst. Differentially customised, efficient derivatives of proline-derived prolinol ether catalysts have catalyzed a wide spectrum of reactions.[3] Diaryl prolinol ether catalysts are reputed as universal catalysts,[4] rendering stereoselectivity from steric repulsion with bulky appendage[5] at C2 (Houk-List model).[6] Even with the recent identification of intermediate species[7] encompassing the structural backbones of the reactants and the organocatalyst, the stereoselectivity still depends upon the electronic and/or steric nature of the C2 appendage.[8] The modifications to the original Jørgensen-Hayashi catalyst have so far seen the enlargement of the C2 appendage. However, recent reports have claimed the downside of the bulkier appendages diminishes the reactivity with sterically bulky substrates,[8] hence the refinement of these catalysts to a more compact version might be of assistance.[4,3] As surprising as may seem, catalyst modifications for sterically hindered substrates, where downsizing the catalyst would be a practical choice have not been reported. In the era of modern organic syntheses, the search for a rational catalyst design can be a resource and time-intensive process, therefore tuning of chiral organocatalysts for steric-specific substrates might be the 'Holy Grail' of rising organocatalysis. Although some of these O-protected prolinol derivatives were found in the literature for different objectives, we intended to synthesize differently O-functionalized prolinols for possible use as

organocatalysts. Synthesis of these catalysts from prolinol or higher-generation prolinols mostly follows a three-step synthetic sequence of -NH protection, O-functionalization and N deprotection with exceptions of single-step silyl protections (owing to strong Si-O bond).[9] Interestingly, the difference in reactivity of NH and OH functionalities in aminols has not been discussed in earlier reports.

A Case Study: Prolinol as nucleophile and Boc_2O as electrophile

The present study originated from the irreproducibility of extensively reported transformations involving Boc protection of Prolinol. Owing to the presence of two nearly similar functional groups i.e. NH and OH groups, functionalization/protection of the NH has preferably been the first step towards almost any synthetic endeavour. BOC-anhydride is a conventional protecting agent for the –NH group because of its easy-to-protect and deprotection protocols. To the best of our knowledge, all previous reports claim exclusive reactivity of the NH group in either basic,[10,11,12] Lewis-acidic[13] or neat[14] conditions to form the N-Boc derivative of prolinol **2a**. As improbable as it may seem, there has been no mention of the competitive O-Boc derivative of prolinol **3a** or the oxazolidinone derivative **4** (Scheme 1). In principle, the chemo-selectivity of an aminol would vary depending on the additives and reaction condition. The relative nucleophilicity of the neutral groups i.e. NH and OH might get reversed with respect to their conjugate bases i.e. alkamide and alkoxide respectively.[15]Although an amine group is generally more nucleophilic than an alcohol group; in presence of a limited stoichiometric amount of an appropriate base, the proton of the hydroxyl group being relatively more acidic than that of the amine group, the alkoxide should form preferably than alkamide, resulting in the reaction of O^- to the electrophile as the anionic oxygen (O^-) would be more nucleophilic than the neutral nitrogen (NH). However, in additive-deprived conditions (neutral nucleophilic sites) or immediacies of a robust base, there might be the formation of both conjugate bases (anionic nucleophilic sites).

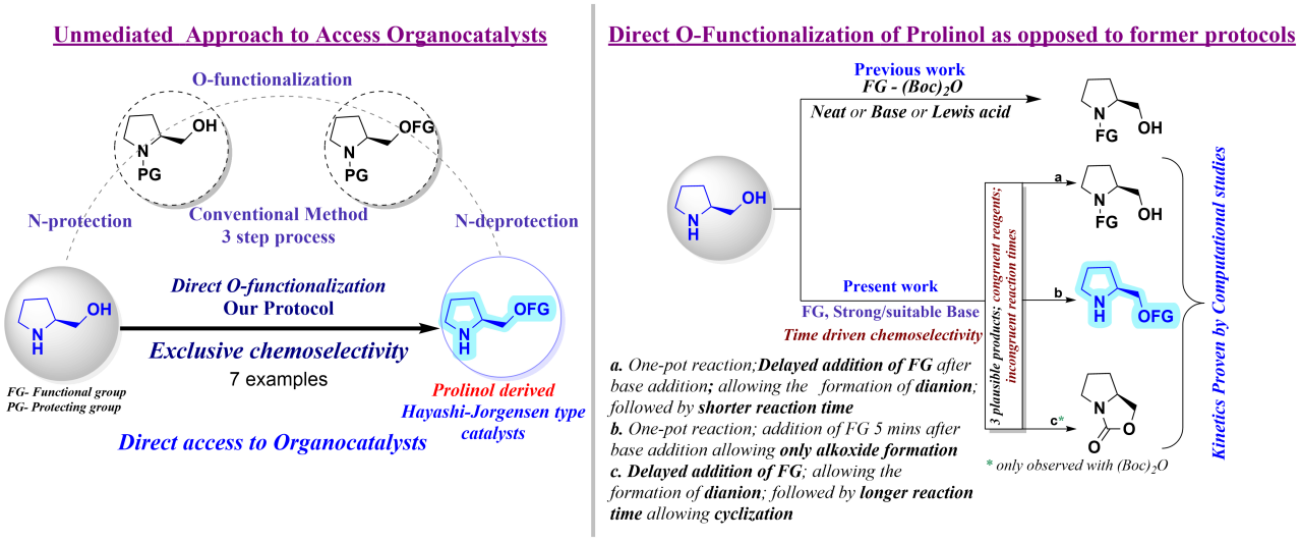
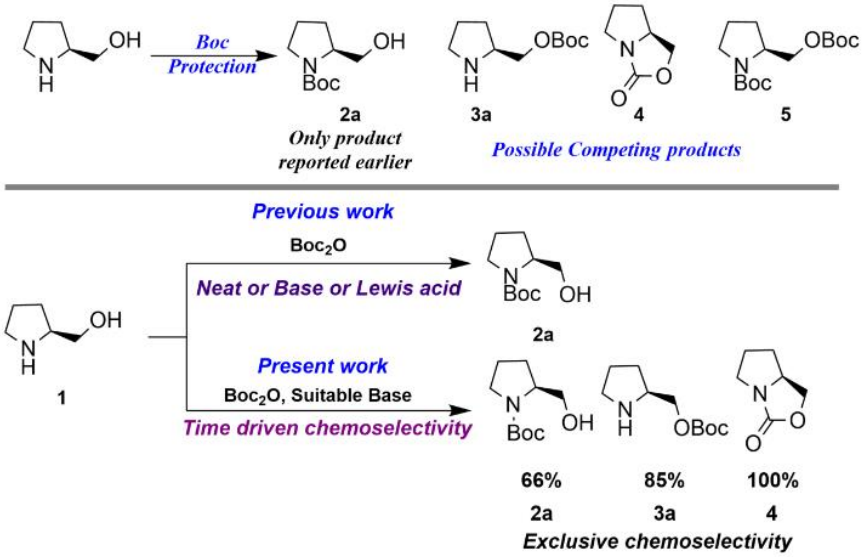


Figure 1. Design plan for chemoselective O-functionalization of prolinol

Given the above circumstances, conceptually an amine group/amide group being more nucleophilic, would react to the electrophile preferably. Contrastingly, in acidic conditions, the amine group would be protonated leaving the alcohol group more reactive towards the electrophile, whereas, in the case of Lewis acids depending upon the propensity of the metal towards N (Nitrogen-philic) or O (oxophilic), the chemoselectivity could be obtained.



Scheme 1. Insights into our work objective

Contrary to the earlier reports, herein we present time-dependent chemoselectivity towards exclusive functionalization of either reacting sites, to synthesize all competing products by exploiting the relative difference in the acidity of the NH and OH group along with the nucleophilicity of their conjugate bases alongside a suitable base.

Results and Discussion

Base Catalyzed Boc protection of prolinol

While attempting straightforward N-Boc protection following a reported protocol[12] using aq. NaOH as the base in tetrahydrofuran (Table 1, Entry 1), N-Boc-(*S*)-prolinol **2a** was observed at only 40% with a considerable amount of a side product, which was characterized as the O-Boc-(*S*)-prolinol **3a** by 1D and 2D NMR (See supporting information for the detailed characterization). The structure was further ascertained by 2D HMBC spectroscopy (Figure 2), which affirms a co-relation between the carbonyl carbon (-***C***=O) and the (–OC***H***$_2$-) protons, through a $^3J_{C\text{-}H}$ interaction, whereas there would be no correlation between the carbonyl carbon (-***C***=O) and the –NC***H***- proton being at a 4-bond distance (No $^4J_{C\text{-}H}$ correlation in HMBC spectroscopy).

Optimization for the chemoselective synthesis of O-Boc-(*S*)-prolinol (3a) in wet solvent

The formation of O-Boc protected (*S*)-prolinol was examined for optimization by using varying equivalence of Boc_2O, different bases such as NaOH/$NaHCO_3$ (different aqueous concentrations), and solvents (THF, Dioxane, MeOH) etc. as shown in Table 1. Contrary to the earlier reports the selectivity was in favour of the OBoc derivative **3a** except in solvent MeOH and Dioxane + Water (1:1) mixture, albeit poor conversion of 9% and 12% respectively (Entries 8 and 9). The best conversion (87%) and chemoselectivity {OBoc **3a** : NBoc **2a** = 86:14} was found in solvent dioxane with excess NaOH (300 mol%) (Table 1, entry 7) in higher molar concentration (3M in H_2O). [16,17]

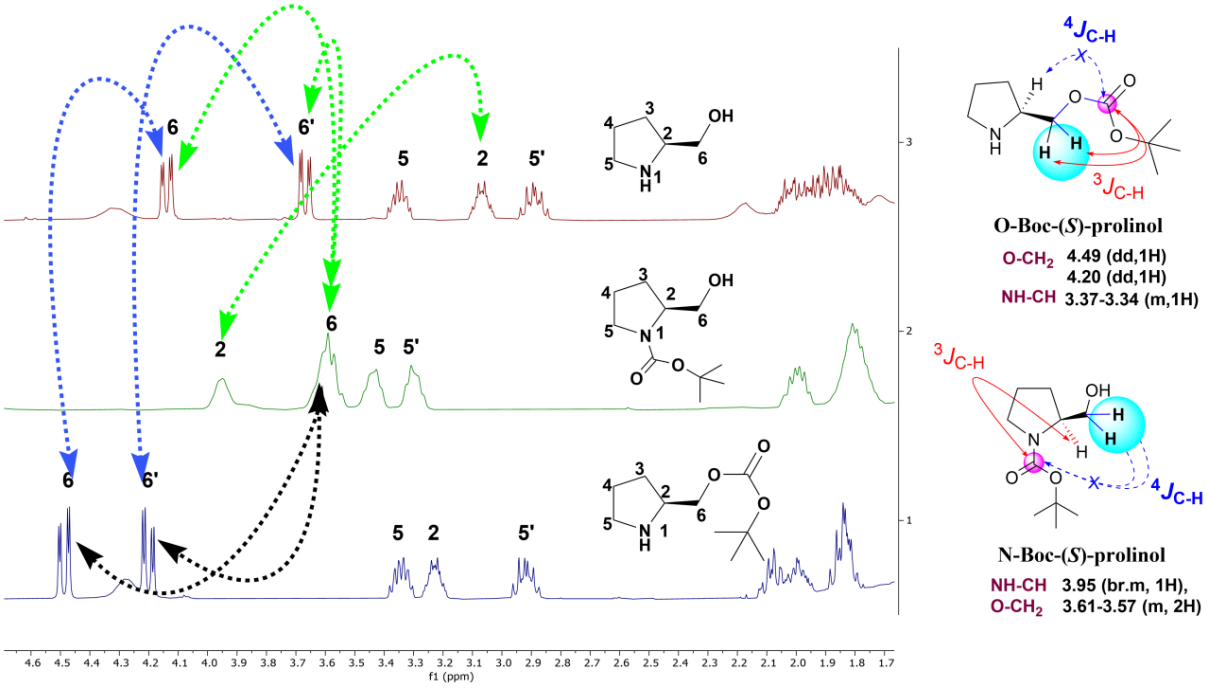
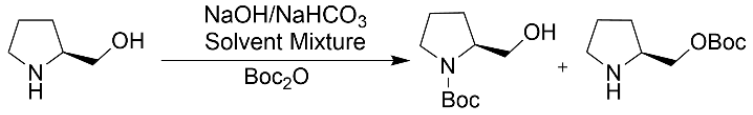


Figure 2. Characterisation of Boc-derivatives of Prolinol; Characteristic HMBC correlations for O-Boc-(*S*)-prolinol (**3a**) and N-Boc-(*S*)-prolinol (**2a**)

Table 1. Screening table for the Boc protection of (*S*)-prolinol **3a** in presence of aq. $NaOH/NaHCO_3$



1 **2a** **3a**

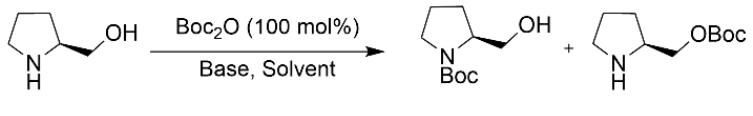
Entry	Base (mol% / 1 M in H_2O)	Solvent	Time (h)	Conversion (%)	Carbamate:Carbonate **(2a:3a)**
1	NaOH[a](100)	THF	23	53	40:60
2	NaOH (120)	THF	24	49	14:86
3	NaOH (200)	THF	23	52	27:73
4	NaOH (120)	Dioxane	22	38	39:61
5	NaOH (200)	Dioxane	23	73	27:73
6	NaOH (300)	Dioxane	24	39	23:77
7	**NaOH (300)[b]**	Dioxane	**37**	**87**	**14:86**
8	NaOH (200)	MeOH	23	9	100:00
9	$NaHCO_3$ (100)	Dioxane: Water (1:1)	24	12	100:00

a) 120 mol% Boc_2O was used b) 3 M in H_2O

Optimization for the chemoselective synthesis of O-Boc-(*S*)-prolinol (3a) in dry solvent

Supposing the poor solubility of Boc_2O in water, the transformation was examined in dry solvents by using varying equivalents of bases (Et_3N/NaH/NaOEt). Interestingly NaH in THF for the reaction was found to be superior to other bases such as Et_3N and NaOEt in both conversion and chemoselectivity (Table 2, entries 8-12) towards the carbonate **3a**. The best-optimized yield for O-Boc-(*S*)-prolinol **3a** was achieved using 300 mol% of NaH (Table 2, Entry 12). In addition, the desired O-Boc-(*S*)-prolinol **3a** could be isolated with 85% yield through column chromatography using neutral alumina.[18]

Table 2. Screening table for Boc protection of (*S*)-prolinol **3a** in presence of Et_3N/NaOEt/NaH in single-phase organic solvent



1 **2a** **3a**

Entry	Base (mol %)	Solvent	Time (h)	Conversion (%)	Carbamate:Carbonate **(2a:3a)**
1	-	DCM	24	55[a]	88:19

2	Et_3N (90)	DCM	29	29	41:59
3	Et_3N (200)	DCM	14	47	30:70
4	Et_3N (200)	MeOH	22	-	-
5	Et_3N (200)	Dioxane	22	30	100:00
6	Et_3N (200)	Dry THF	22	24	79:21
7	NaOEt (200)	Dry THF	21	8	100:00
8	NaH (100)	Dry THF	21	80	06:94
9	NaH (60)	Dry THF	13	71	01:99
10	NaH (20)	Dry THF	24	28	25:75
11	**NaH (300)**	Dry THF	**13**	**100 (70%)[b]**	**02:98**
12	**NaH (300)**	Dry THF	**2**	**100 (85%)[b]**	02:98

a) For more screening without additives, please refer SI, b) isolated yield

Mechanistic investigation/inquisition onto the chemoselective mono-Boc protection of (*S*)-prolinol

The discrepancy found in our result regarding the formation of exclusive/major O-Boc product **3a** as against the literature precedence prompted us to study the mechanistic intricacies in the process. It was imperative to address, the preferred elemental steps leading to the selectivity, along with contingent pathways to alter the selectivity towards other adversary products. Figure 3 summarizes the competing elementary pathways towards the formation of the carbonate **3a**/carbamate **2a**/oxazolidinone **4** derivatives of (*S*)-prolinol. There are two elementary steps involved in the formation of carbonate **3a**/carbamate **2a**: *i)* Proton abstraction from OH/NH to form the conjugate bases **Int-I**/**Int-II**; *ii)* Nucleophilic attack of the conjugate base N^-/O^- to the electrophile (Boc_2O). Step 1 and step 2 are contesting pathways for the initial "proton abstraction" by NaH to form the conjugate bases **Int-I** and **Int-II**. The chemoselectivity of the reaction can be controlled at this confluence if a suitable base can differentiate the abstraction of proton alongside the enhanced nucleophilicity of the anionic conjugate base, over the competing neutral acidic nucleophile, making the proceeding attack to the electrophile (Boc_2O) selective. Step-3 and step-4 describe the competing pathways of the reaction amongst the conjugate alkoxide base with Boc_2O and the second proton abstraction (supposing step-1/step-

2 are not selective or in presence of excess base) to form the dianion species **Int-III** respectively. Step-5 and step-6 involve similar competition as step-3 and step-4, but with the corresponding amide/alkamide conjugate base. Presuming that the dianion **Int-III** forms, the chemoselectivity would depend on the nucleophilicity difference of the conjugate bases N^-/O^- to the Boc_2O (step 7 vs step 8) followed by quenching to form the mono-Boc derivatives. Moreover, at this point, there is a probability of cyclisation of the anionic mono-Boc intermediate **Int-IV**/I**nt-V** to form the oxazolidinone derivative **4**.

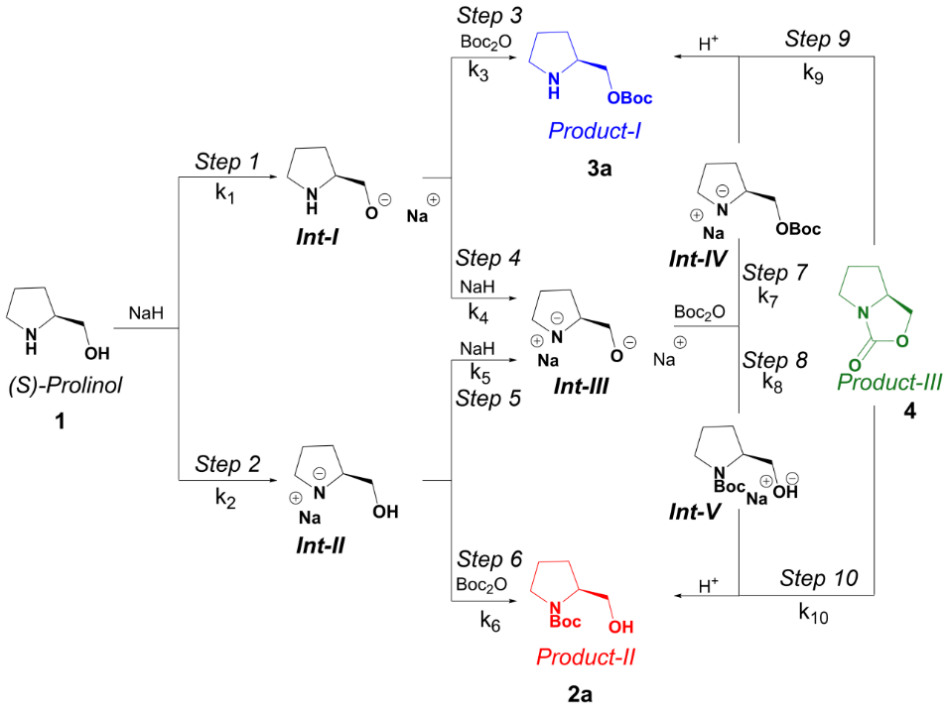


Figure 3. Competing elemental pathways for the Chemoselective functionalization of (*S*)-prolinol and the kinetics therein

Controlled experiments to establish the preferred elementary steps

As mentioned in Figure 3, different sets of experiments were performed with varied equivalents of reagents, reaction time, the time interval between the additions of reagents etc. to establish the trail leading to the aspired product.

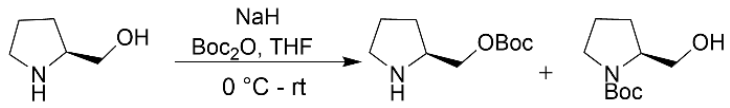
Initial selective formation of conjugate bases Int-I over Int-II (Step 1 vs step 2) - Chemoselective synthesis of the carbonate

To establish the favoured preliminary step among steps 1 and 2, a 1:1 stoichiometric reaction between NaH and (*S*)-prolinol **1** was set

(Table 3, Entry 1), which resulted in excellent selectivity (O-Boc **3a**: N-Boc **2a** = 90:10) towards the O-Boc compound **3a** in very good conversion (90%). Even with an excess of NaH

(Table 3, Entries 2-4), the chemoselectivity was excellent and in favour of the carbonate formation. These controlled experiments clearly suggest the kinetic favourability of step-1 and also step 1 + step 3 over step-2 ($k_1 > k_2$ and $k_1+k_3 > k_2$). It could also be substantiated that $k_3 > k_2$ for the reason that once the alkamide ion forms, retrogression of reactivity favours the formation of the carbamate (Table 4). The amine proton in this particular case seems hard to be abstracted by the suitable base NaH, which is responsible for the chemoselectivity. This is well in accordance with the lower pK_a of the hydroxyl group (30.8) in comparison to the amine group (43.9) observed computationally. (For more details, refer SI).

Table 3. Chemoselectivity towards the formation of carbonate



1 **3a** **2a**

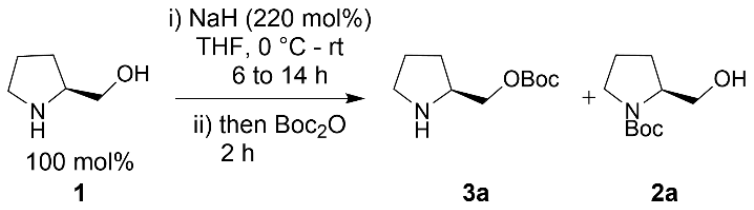
Entry	NaH mol%	Time (h)	$(Boc)_2O$ mol%	Conversion	**2a:3a**
1	100	63	100	90	10:90
2	300	2.5	100	100	07:93
3	220	4	100	100	07:93
4	300	70	200	100	11:89

The disparity in sensitiveness of the conjugate basic sites alkoxide vs alkamide/amide (Step 7 vs step 8); Chemoselective synthesis of the carbamate

Conceptually an amine group would be more nucleophilic than a hydroxyl group. In addition, there is literature precedence about carbamate selectivity without any additives. In our hand, although we did get good selectivity towards the carbamate, the conversion was poor, with the best conversion being 55% (Refer SI, Table S3). Envisioning the reversal of nucleophilicity order, in case the dianion **Int-III** can be synthesized, controlled experiments are executed. Although the alkoxide formation was preferable over the alkamide formation (Figure 3), the reaction was attempted with excess NaH (220 mol%) and lengthened reaction time preceding the addition of the electrophile (Boc_2O) to impel the dianion formation. Interestingly, when the addition of Boc_2O was delayed by 7 h (Table 4, Entry 1), the N-Boc product **2a** was obtained as the major product conversion: 81%, N-Boc: O-Boc = 81:19). The chemoselectivity obtained here could be explained and attributed to the fact that N^- is a better nucleophile that O^-. As O-Boc forms faster, the 19% O-Boc compound was assumed to have formed from the mono-anion, i.e. alkoxide ion. Motivated by the reversal of selectivity, the reaction was subjected to optimization. Hence, in another reaction, the addition of Boc_2O was delayed further (14 h,

Table 4, Entry 2). Confirming our assumption, the reaction resulted in exclusive N-Boc protection [N-Boc **2a**: O-Boc **3a**= 100:0], where product **2a** could be isolated in a good 66% yield.

Table 4. Reaction with excess NaH (220 mol%) and delayed addition of Boc_2O



100 mol%

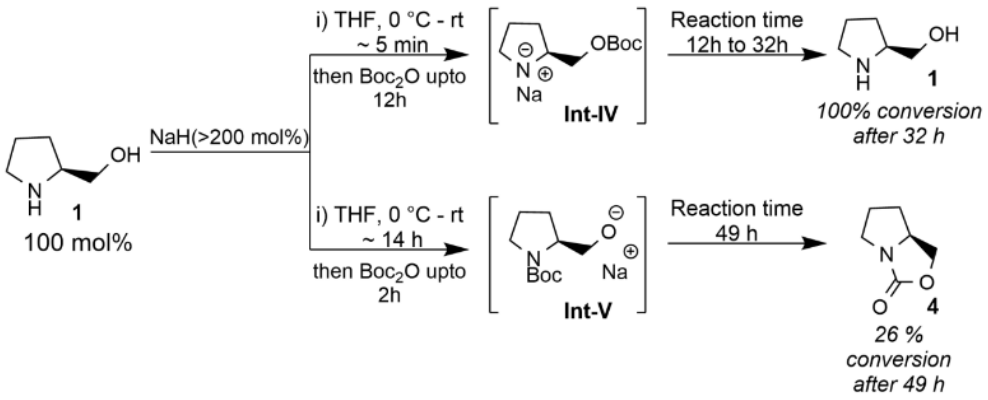
1 **3a** **2a**

Entry	NaH Reaction time (h)	$(Boc)_2O$ (mol%), Reaction time (h)	Conversion	**2:3**
1	7	100, 2	91	81:19
2	14	120, 2	100	100:0 (66%*)

*Isolated yield

Delayed addition of Boc_2O in tandem with extended reaction time, steering the chemoselective synthesis of oxazolidinone (4)

The reaction condition leading to the formation of the carbamate derivative, led to the formation of oxazolidinone **4** upon temporizing to quench it, whereas the condition leading to the formation of the carbonate, regressed to prolinol over delayed quenching. This set of reactions unravelled the critical nature of the reaction condition toward successful syntheses of the mono-Boc compounds. A similar phenomenon was also observed when the pure mono-Boc compounds **2a** and **3a** were individually treated with NaH in dry THF (For more details see SI, Scheme S3). In concert, it also gave the fate of the mono-Boc compounds towards NaH, along with the successful synthesis of oxazolidinone **4** (Scheme 2). The poor conversion to oxazolidinone could be improved to 100% by replacing Boc_2O with diethyl carbonate (For details see SI, Scheme S4).

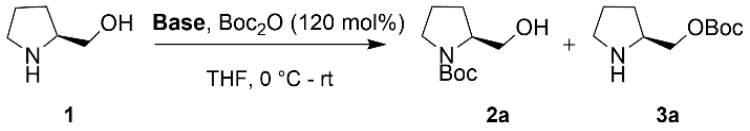


Scheme 2. Deprotection of O-Boc compound with a base

Screening of Bases

It was apparent that a strong base is essential for excellent chemoselectivity. Further, we screened other strong bases like BuLi, LDA, and LiHMDS.

Table 5. Base screening



1 2a 3a

Entry	Base / mol%	Time (h)	Conversion (%)	Carbamate:Carbonate **(2a:3a)**
1	NaH	2	100	02:98
2	LDA /300	3	100	00:100
3	BuLi / 300	3	100	100:0
4	BuLi / 100	4	100	08:92
5	LiHMDS / 100	1	100	02:98

*p*Ka comparison of used bases: BuLi (50) > LDA (36) = NaH (35) > LiHMDS (26*)*

Like NaH, 300 mol% of LDA resulted in complete conversion to O-Boc prolinol. However, the reaction with 300 mol% of BuLi resulted in the N-functionalized compound, further explaining the quick possibility of the dianion (**Int-III**) formation with the robust base with *p*Ka 50 and reacting from the more nucleophilic N-site. When the reaction was tried with a stoichiometric amount of BuLi (100 mol%), 92% conversion was found towards the O-functionalized prolinol. The reaction with 100 mol% LiHMDS resulted in 98% conversion to O-Boc prolinol.

Proposed Pathways for chemoselective either Boc Protection of Aminols

Concisely, base-mediated chemoselective mono-Boc protection of aminols is described in (Figure 4). For the first equivalent of NaH, the -OH group is deprotected preferably over NH ($k_1 > k_2$) to form the alkoxide ion which reacts with Boc_2O to form an exclusive O-Boc derivative (**2a**:**3a** up to 2:98). The reaction has even been very successful with higher equivalents of NaH (100 to 300 mol%) and Boc_2O (100 to 200 mol%), confined to shorter time intervals (~ 5 min) between the addition of NaH and Boc_2O to suppress the formation of dianion. The reaction ought to be quenched in under 11 h when complete (monitored by TLC, For further details refer to SI, Figure S2), to suppress the deprotection of the O-Boc functional group back to the precursor aminol **1**. Even in the case of excess NaH, the contesting elementary step 3 (Boc protection of the alkoxide) is a swifter process than step 4 (dianion formation of the alkoxide) ($k_3 > k_4$) which is conclusive from the exclusive formation of O-Boc compound in Table 3, supplemented by $k_8 > k_7$ (Table 4). When the dianion (**Int III**) formation was compelled with surplus NaH (> 200 mol%) over a longer time and in the absence of Boc_2O, the dianion reacted with Boc_2O chemoselectively at the N^- furnishing N-Boc product singularly. This imparts that elementary step 7 is sluggish as compared to step 8. The presumptive pathway for the O-Boc protection is Step 1 followed by Step 3, whilst for N-Boc is Step 1 followed by step 4, and then step 8. It was also interesting to find the formation of oxazolidinone **4** if quenching of **Int-V** was delayed up to 49 hours (Scheme 2).

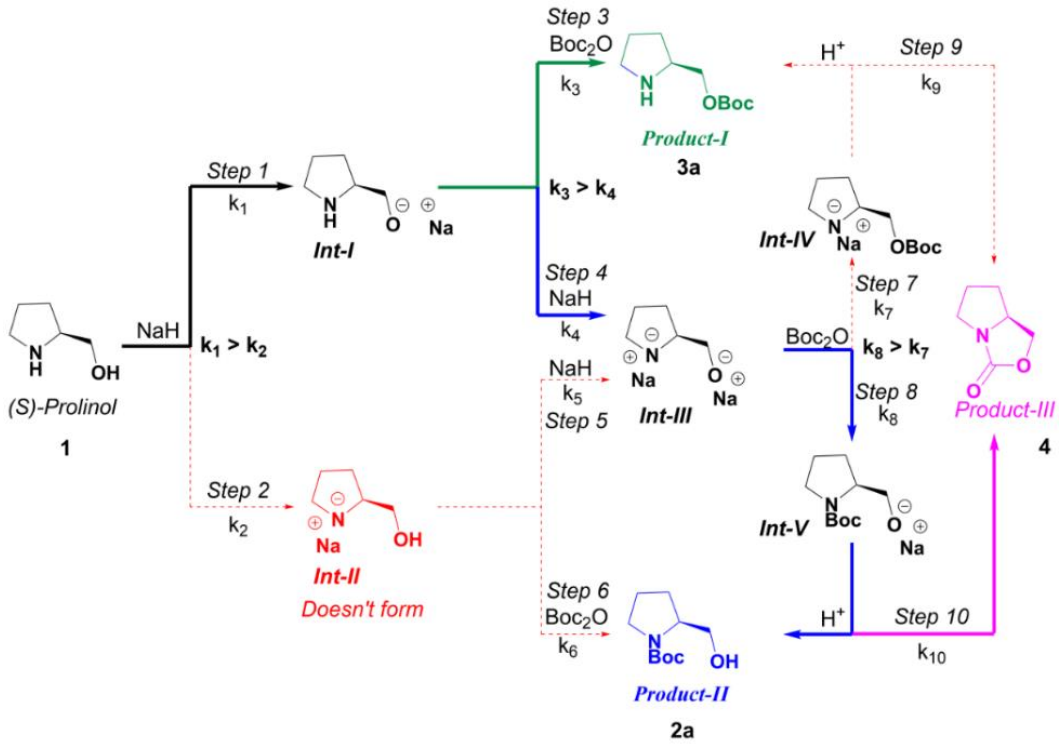


Figure 4. Proven pathways for the chemoselective formation of either Boc derivatives

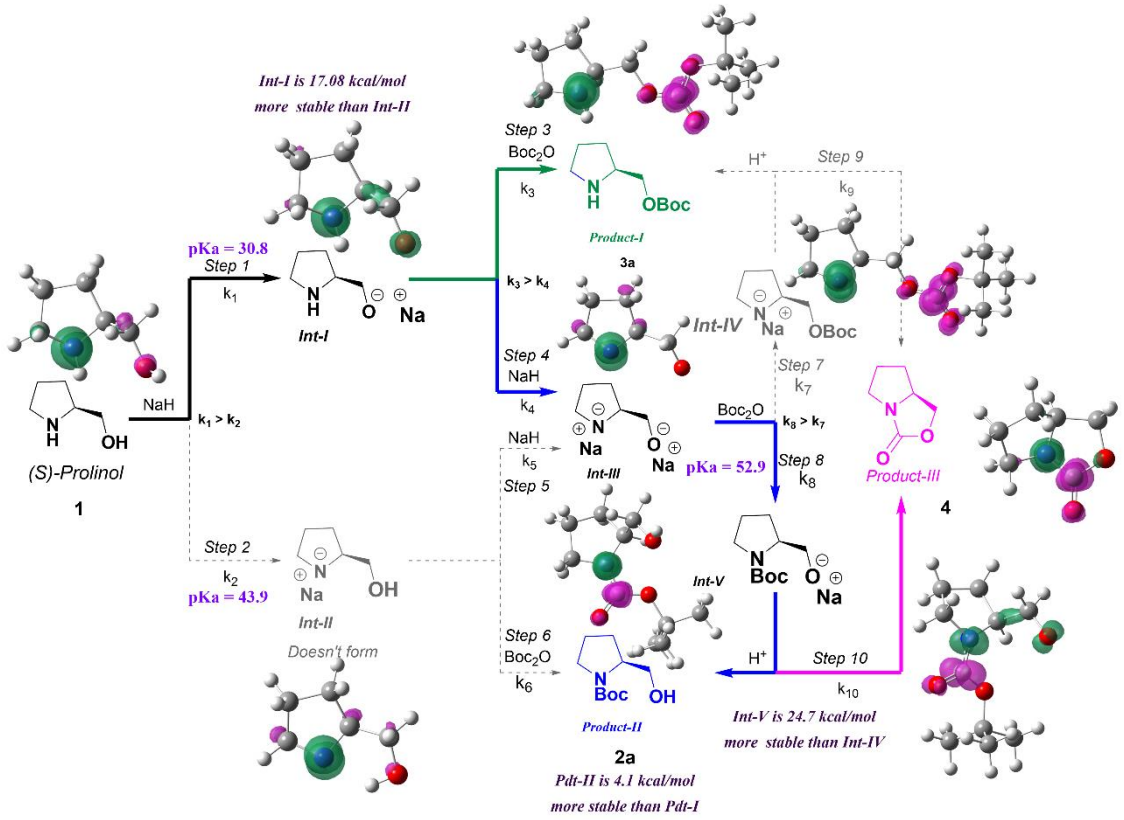


Figure 5. Computational investigation of each elemental step with a) pKa of protic sites; b) relative stability of intermediates; c) electron density of the active sites (-nucleophilicity, -electrophilicity)

Computational Findings

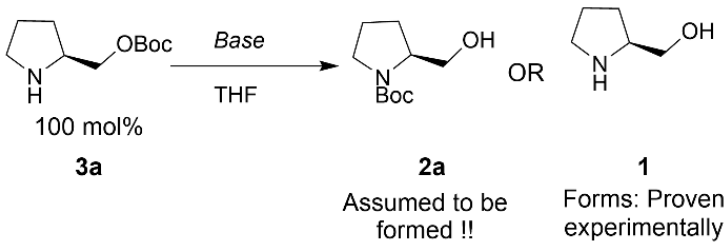
To get more insights into the proposed pathway, computational analysis of the total reaction pathway was assessed by considering the stability of each intermediate and product (Figure 5). In addition, the nucleophilic sites were compared for evaluation towards the electrophile. The formation of **Int-I** is much faster than **Int-II** because of their difference in *p*Ka values. The calculated *p*Ka for **Int-I** (30.8) was found to be lower than that of **Int-II** (43.9). Moreover, we found that **Int-I** is also more stable than **Int-II** by an energy value of 17.08 kcal/mol. This along with the higher nucleophilicity of alkoxide ion over NH, support the formation of O-Boc product rather than N-Boc product in presence of Boc_2O and NaH. The second proton abstraction from **Int-I** to form a di-anionic **Int-III** is also not easy because of the very high *p*Ka (52.9) which correlates with the findings $k_3 > k_4$. However, once the dianion forms, **Int-V** forms very quickly because of its higher stability (24.7 kcal/mol) than **Int-IV**. The calculation of dual descriptor (details are given in SI) on **Int-III** confirms the higher nucleophilic nature of N over O which also supports the formation of **Int-V** and subsequently the formation of the N-Boc product. Interestingly we have observed that the N-Boc product **2a**

is 4.1 kcal/mol more stable than the O-Boc product **3a** (Please refer to SI for further information).

Mechanistic debate over carbonate/carbamate formation with Boc_2O

Mechanistically, there are assumptions that either a) the reaction leads to the formation of di-Boc-prolinol **5** followed by the subsequent decomposition of the unstable carbonate in situ/during work-up or b) the carbonate **3a** is formed first during the reaction of prolinol with Boc_2O and eventually gets rearranged to the more stable carbamate, although there is no experimental evidence in favour of these mechanistic proposals. With earlier controlled reactions, even with an excess of base di-Boc-prolinol **5** was never obtained, and the mono-Boc compounds **2a** and **3a** over longer reaction time resulted in the oxazolidinone **4** and prolinol **1** respectively. To check the intramolecular rearrangement of carbonate to carbamate, synthesized carbonate **2a** was exposed to various basic conditions. Interestingly the carbonate was found to be disintegrated to prolinol rather than the earlier assumed carbamate. These experiments might indicate the re-evaluation of the earlier assumed mechanistic details for the formation of the N-Boc-prolinol **2a**.

Table 6. Fact or Fiction

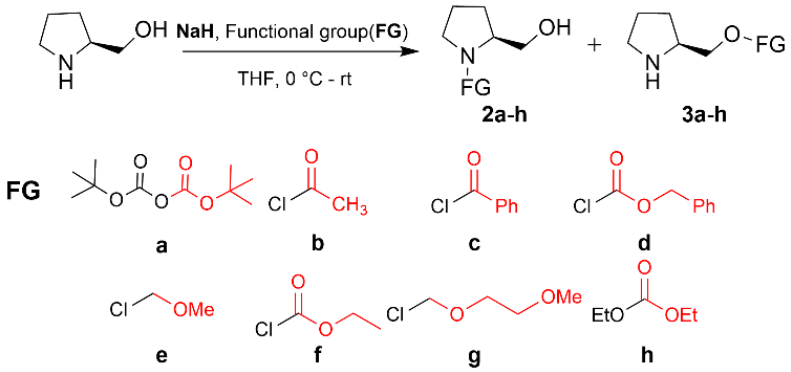


Entry	Base/mol%	Time (h)	Conversion (%)	Ratio (**2a**:**3a**:**1**)
1	NaOEt /100	4	64	0:36:64
2	NaOH (3M)/ 100	5	8	0:52:48
3	NaH/ 100	5	00	0:0:100

Unmediated Syntheses of prolinol-derived Organocatalysts

The above protocol paved a way for the direct syntheses of prolinol-derived catalysts,[19,20,21] which would provide alternative less-bulky organocatalysts to that of Hayashi-Jørgensen catalysts and could prove influential in asymmetric organocatalyzed reactions. A few organocatalysts with a variety of functional groups i.e. ethers, esters, and carbonates have been synthesized with good to excellent yields (Table 7). (Please refer to SI for further information)

Table 7. Substrate scope for the direct O-functionalization of prolinol



Entry	Electrophile/ mol%	mol% (NaH)	Time (h)	Conversion (%)	Isolated Yield
1	Boc anhydride	300	2	100	85%
2	Acetyl chloride/150	450	4	72	55%
3	Benzoyl chloride/110	200	2	88	64%
4	Benzyl chloroformate/100	100	2	73	34%
5	MOM-Cl/100	300	4	100	50%
6	Ethyl chloroformate/100	220	2	77	60
7	MEM-Cl/100	220	1	100	53
8	Di-ethyl carbonate/ 120	300	4	-	-

*Isolated yield; a) Benzyl alcohol spot overlaps with the product spot in most fractions, hence poor yield

Conclusion

In essence, never reported before O-Boc-(*S*)-prolinol **3a** was noticed in the Boc protection of (*S*)-prolinol (**1**) with various base-mediated reactions. The elementary steps for the mono-Boc protection were studied through controlled experiments to address the discrepancy between our results with the literature reports. It was stimulating to find the large difference in reactivity of the competing processes such as *a)* formation of the conjugate bases (k_1 vs k_2); *b)* alkoxide to O-Boc/dianion (k_3 vs k_4); *c)* dianion to O-Boc/N-Boc (k_7 vs k_8); *d)* affinity of NaH towards carbonate/carbamate carbonyl; *e)* affinity of NaH towards Carbonate/NH etc. to give premium selectivity. The comprehension of the integral steps led us to find the optimized condition for the exclusive N-Boc protection of (*S*)-prolinol (**1**) by delaying the addition of Boc_2O. Furthermore, the synthesis of O-Boc-(*S*)-prolinol (**3a**) has been optimized to 85% isolated yield and characterized thoroughly through 1D and 2D NMR spectroscopic data. N-Boc-(*S*)-prolinol (**2a**) could be synthesized in 66% yield. Base-catalyzed deprotection of O-Boc functionality was perceived, whereas N-Boc functionality routed the formation of oxazolidinone, confirming the passive abstraction of -NH proton as opposed to the deprotection of the O-Boc compound **3a**. The other competing product oxazolidinone **4** could

also be synthesized exclusively, starting from (*S*)-prolinol **1**, which recurrently proved the superior elementary steps. As attainable as it may seem, conception to implementation can be labour and time intense. Effectively we have synthesized prolinol-derived organocatalysts through this unmediated chemoselective O-functionalization of prolinol. The leverage of this protocol is the two-step reduction in the synthetic route as opposed to former protocols, which makes it a more sustainable approach. Direct O-functionalization of the prolinol also could pave way for easy access to compact prolinol-derived Hayashi-Jørgensen type catalysts to assist asymmetric organocatalytic reactions. The protocol has been extended to be successful with seven substrates along with some newly reported substrates of prolinol (O-Boc **3a**, O-Bz **3c**, O-CBz **3d**, and O-ethyl carbonate **3f**) in good to excellent yields. In addition, this work highlights an established reaction protocol and its sensitivity to the reaction conditions alongside the utilisation of 2D spectroscopy (HMBC), for the identification of the obtained substrates. Detailed study of these catalysts in asymmetric organocatalytic reactions is in progress in our laboratory.

Author Contributions

JS designed, performed and analysed all the experimental work, JP contributed to the initial screening and scale-up of materials, SG performed the computational calculations, JS, GS conceptualised the project and drafted the article. All authors contributed to the critical revision of the manuscript before the submission of the final version of the article.

Conflicts of interest

"There are no conflicts to declare".

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