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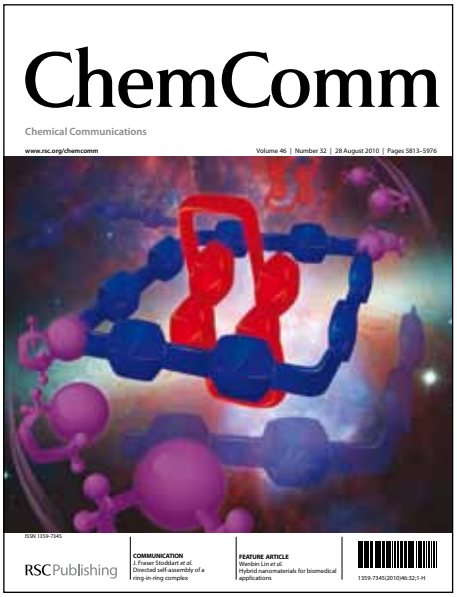

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Counterion Effects in the Catalytic Stereoselective Synthesis of 2,3′-Pyrrolidinyl Spirooxindoles

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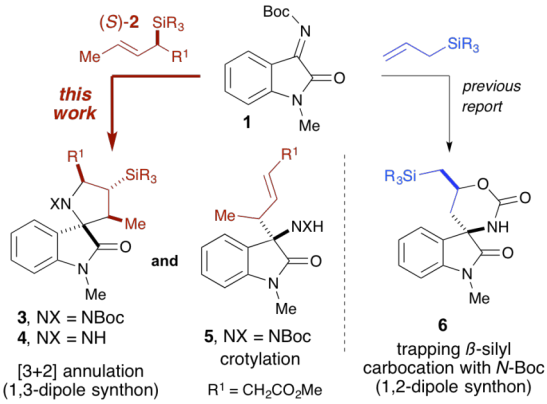
A Lewis acid-catalyzed stereoselective [3+2] annulation of crotylsilanes with iminooxindoles is reported to access 2,3'-pyrrolidinyl spirooxindoles with four stereocenters. The addition of NaBArF significantly enhances reactivity, allowing either metal salts or acidic clay to be effective catalysts for the stereoselective reaction.

Based on their occurrence in natural products, spirocyclic oxindoles are an attractive three-dimensional structure often considered a privileged scaffold for the discovery of new medicinal compounds.[1-4] In particular, spiropyrrolidine oxindoles have shown an important array of biological activity.[5-7] Elegant synthetic routes have been reported for the stereoselective synthesis of 3,3'-spiropyrrolidine oxindoles,[8-11] while the synthesis of 2,3'-pyrrolidinyl spirooxindoles remains less developed.[12,13] Herein we report the catalytic stereoselective synthesis of 2,3'-pyrrolidinyl spirooxindoles containing four stereocenters via a [3+2] annulation between an enantioenriched crotylsilane and *N*-Boc-iminooxindoles. This reaction represents the first example of allylic silanes in the synthesis of spiropyrrolidine oxindoles and also provides a unique platform to compare counterion effects on the activity and selectivity of Lewis acidic metal salts and heterogeneous clay catalysts.

Allylic silanes are versatile nucleophiles[14] that can function as [1,2]-dipole[15, 16] and [1,3]-dipole[17, 18] synthons for efficient access to functionalized heterocycles and carbocycles. Due to their mild nucleophilicity,[14] reactions with allylsilanes generally require the use of Lewis or Brønsted acids.[19, 20] Previously, Panek and co-workers have utilized reactions of enantioenriched crotylsilanes (e.g. **2**) with in situ-derived iminium ions for selective pyrrolidine formation.[21-23] In an attempt to access spiropyrrolidines such as **3**, we investigated Lewis acid-catalyzed spirocyclization of allylsilanes with *N*-Boc iminooxindoles (**1**); however, instead of accessing the pyrrolidine, this reaction produced novel spirocyclic carbamate oxindoles **6** via *N*-Boc trapping of the *β*-silyl carbocation intermediate (Scheme 1).[24] In continued pursuit of spiropyrrolidines, we turned to investigate the use of crotylsilanes and to identify the elements controlling reactivity and product selectivity.



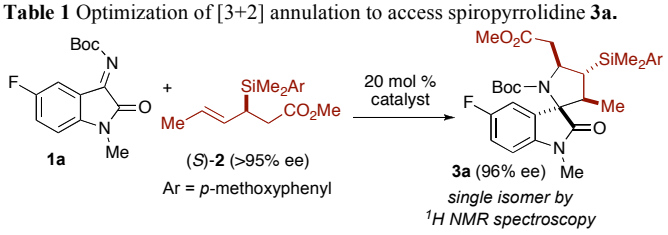
Scheme 1. Product selectivity for reactions of allylic silanes with iminooxindoles

We identified that several Lewis acidic metal salts catalyze the annulation of (*S*)-crotylsilane **2** with *N*-Boc-iminooxindoles **1** to afford *N*-Boc spiropyrrolidine **3** as a single diastereomer as judged using ^{1}H NMR spectroscopy (Table 1). A mixture of annulation (**3**) and crotylation (**5**) was observed depending on the catalyst and temperature; however, solely the [3+2] mode of annulation was observed with no trace of the spirocarbamate product. While $Sc(OTf)_3$ showed good reactivity (e.g. 3h), the *N*-Boc crotylation was also observed (entry 1). Metal chloride

salts afforded selective formation of the spiropyrrolidine, albeit with low reactivity (c.f. 168h, entry 2).

The addition of sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (NaBArF) significantly enhanced the reaction rate, allowing several metal salts to catalyze the spirocyclization reaction with the competing crotylation observed (entries 2-8). Triflic acid (at –78 ºC) also afforded a mixture of the annulation and crotylation products (entry 10). The optimal conditions were identified as $CuCl_2$/NaBArF at –20 ºC where the crotylation was not observed.[21] The enhanced reactivity with NaBArF is attributed to formation of a cationic metal complex, with a more diffuse counterion affording a higher the yield (entry 8 vs 9). The reaction is highly stereoselective and the absolute stereochemistry has been assigned based on the starting configuration of the crotylsilane and reaction via anti-S_E' addition.[21, 22,25] The relative stereochemistry of spiropyrrolidine **4a** was confirmed by nOe experiments,

Table 1 Optimization of [3+2] annulation to access spiropyrrolidine **3a.**

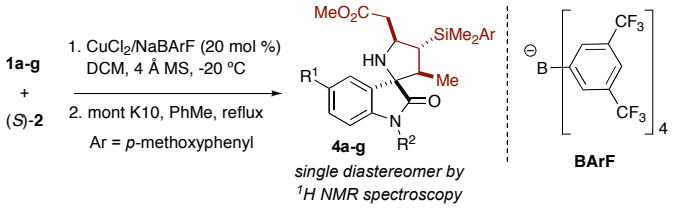


entry	catalyst	counterion Source[a]	temp (˚C)	time (h)	yield of **3a** (%)	yield of **5** (%)
1	$Sc(OTf)_3$	--	23	3	61	8
2	$ScCl_3$	--	23	168	37	0
3	$ScCl_3$	NaBArF	23	22	61	14
4	$InCl_3$	NaBArF	23	5	42	0
5	$ZnCl_2$	NaBArF	23	72	61	17
6	$SnCl_2$	NaBArF	23	12	51	31
7	$CuCl_2$	NaBArF	23	2	64	27
8	$CuCl_2$	NaBArF	-20	24	79	0
9	$CuCl_2$	$NaSbF_6$	-20	72	41	0
10	TfOH	--	-78	20	68[b]	10[c]

[a]Reaction performed with 22 mol % of counterion source. [b]NH spiropyrrolidine was also isolated in 8 % yield. [c]Crotylation product isolated as an unprotected 3-aminooxindole (see supporting information).

We then investigated the scope of the *N*-Boc-iminooxindoles in the spiropyrrolidine annulation reaction with the Cu(II)/BArF catalyst (Table 2). Various substituents on the oxindole backbone can be employed with yields ranging from 79–88 % (Table 2, entries 1-4). Phenyl and benzyl substitution on the 1-postion also proceeded with comparable yields (entries 5, 6); however, the *N*-acyl (**1g**) and free *N*-H oxindole (**1h**) did not afford any product, presumably due to competitive binding of the oxindole substrate to the copper catalyst (entries 7, 8). Deprotection of the Boc group was accomplished using montmorillonite K10 to access *N*-H pyrrolidines **4**, which were isolated as pure material upon simple filtaration.[26,27]

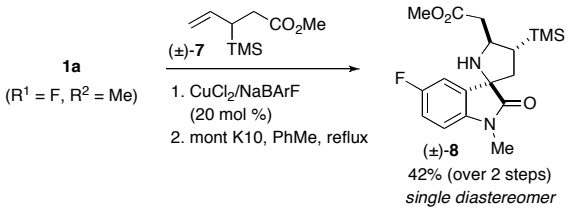
Table 2 Scope of imine in crotysilane annulation.



entry	R^1	R^2	product	yield of **3** (%)[a]	yield of **4** (%)[a]
1	F	Me	**4a**	79	90
2	H	Me	**4b**	80	85
3	MeO	Me	**4c**	88	66
4	Cl	Me	**4d**	81	99
5	H	Ph	**4e**	88	80
6	H	Bn	**4f**	53	93
7	H	Ac	**4g**	0	--
8	H	H	**4h**	0	--

[a] Isolated yield.

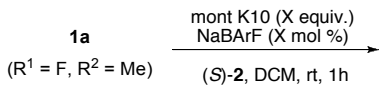
The selective formation of spiropyrrolidine **3** without *N*-Boc trapping of the β-silyl carbocation (i.e. spirocarbamate formation) is attributed to factors stabilizing the transient β-silyl carbocation intermediates in the pathway.[28-3031] Overall, the [1,2]-silyl shift must be favored relative to trapping by the *N*-Boc group. An α-substituent enhances stability of the β-silyl carbocation formed as the result of the 1,2-silyl shift. The ester group may also contribute to the stabilization of the initial β-silyl carbocation via a 5-membered ring chelate and may block interactions with the *N*-Boc group. In order to test the role of the ester substituent, we investigated the reaction of allylsilane **7**, which lacks the alkene substitution and has a smaller silyl group. Indeed, this reaction still afforded spiropyrrolidine **8** as a single diastereomer as judged by ^{1}H NMR spectroscopy, with no spirocarbamate observed (Scheme 2).



Scheme 2. Testing substituted allylsilanes for product selectivity.

Based on the significant activating effect of NaBArF for metal chloride catalysts, we investigated the activity of montmorillonite K10 as a solid Lewis acid catalyst with NaBArF as a co-catalyst to promote the formation of 2,3'-spiropyrrolidine oxindoles. Although montmorillonite has been reported to mediate the Hosomi-Sakurai reaction,[32] there are no examples of allylsilane annulation reactions catalyzed with solid Lewis acids. Montmorillonite offers many advantages over traditional metal salt catalysts, because it is inexpensive, easy to handle, reusable and eco-friendly.[33] Although the use of cation-exchanged montmorillonite is well explored[34], the use of homogeneous co-catalysts is relatively unexplored.

Table 3 Montmorillonite–promoted synthesis of spiropyrrolidine oxindoles.

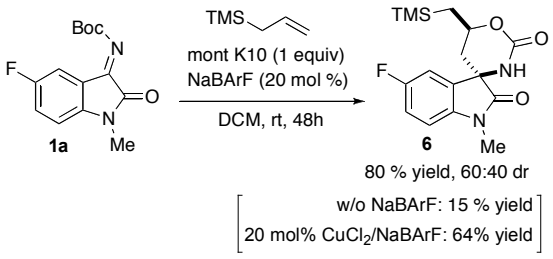


entry	mont. K10 (equiv)	mol % NaBArF	yield (%)[a]
1	1.0	0	0
2	1.0	20	60[b]
3	0.5	20	29
4	1.0	40	56
5	1.0	20	64[c]
6	1.0	20	53[d]

[a]Isolated yield. [b]Average of two yields. [c]Reaction performed at 4 ºC. [d]Reaction performed in $CHCl_3$.

We discovered that the addition of NaBArF with montmorillonite is also successful to promote the stereoselective synthesis of spiropyrrolidine **3**. The reaction affords a single diastereomer of spiropyrrolidine **3**, with no crotylation (**5**) or spirocarbamate (**6**) observed. In the absence of NaBArF, only deprotection/degradation of the iminooxindole starting material was observed (Table 3, entry 1). Although the rate of spirocyclization is fast (<1h), the degradation of iminoisatin persisted under all reaction conditions, despite investigation of severl reaction variables (entries 2-6). We also demonstrated that montmorillonite/NaBArF conditions efficiently promote the spirocyclization of allyltrimethylsilane with imine **1a** to afford spirocarbamate **6** in 80% yield with a 60:40 diasteromeric ratio (Scheme 3). Mechanistic studies and catalyst recovery are underway to determine the role of NaBArf with montmorillonite.[35]

Because NaBArF has a significant activating effect for both the metal chloride salt and the acidic clay, we propose that the Lewis acid (either metal salt or clay) activates the iminooxindole electrophile while NaBArF acts as a co-catalyst by contributing to the stabilization of the transient β-silyl carbocation intermediate.[28, 36, 37]



Scheme 3. Spirocarbamate formation using mont. K10 and NaBArF.

In conclusion, we have developed the first stereoselective synthesis of 2,3'-pyrrolidinyl spirooxindoles using a crotylsilane reagent. The reaction utilizes mild, environmentally-friendly conditions with either $CuCl_2$ or montmorillonite clay with NaBArF as an co-catalyst to efficiently produces a complex core structure with 4 stereocenters. The structure of the allylic silane with a stabilizing methyl ester substituent controls selective formation of the spiropyrrolidines. The role of NaBArF as an activator for the montmorillonite-promoted annulation reaction suggests that co-catalysts and additives can have a significant effect to enhance the activity and selectivity of heterogeneous clay catalysts to promote new reactions.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data for all compounds.

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