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Highly regio- and stereocontrolled synthesis of β-substituted α-tributylstannyl enamides

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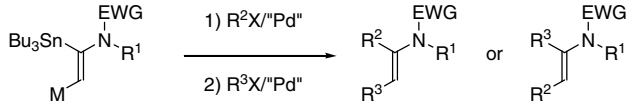
Abstract—The regio- and stereocontrolled synthesis of β-substituted α-stannyl enamides is reported starting from internal ynamides. The synthesis of new ynamides as well as bis-ynamides is also described. Finally first examples of successful cross-coupling to afford α/β-disubstituted enamides are also reported.

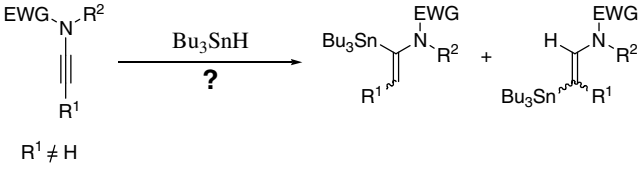
One of the main challenges in the synthesis of α,β-disubstituted enamides is the stereocontrol of the double bond. Coupling of alkenes[1], halogeno-alkenes[2] or enol sulfonates[3] with amines usually gives excellent stereocontrol and yields but this approach is mostly limited to specific alkenes. We have recently described the stereocontrolled synthesis of α,β-stannyl and α-stannyl β-silyl enamides.[4] A stepwise coupling of these two carbon-metal bonds should in principle yield stereodefined α,β-substituted enamides (Scheme 1). Unfortunately, despite numerous efforts in this area, no satisfactory results have been obtained.[5]



M = $SnBu_3$ or $SiMe_3$

Scheme 1. Attempted couplings of bis-metallated enamides.

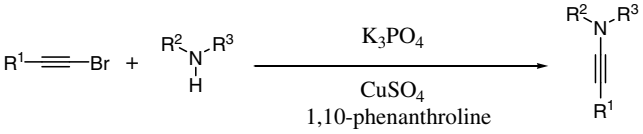
Therefore, we decided to turn our attention to a slightly different approach in which the substituent at the β-carbon is introduced at a very early stage of the synthesis. This means that we have to start from 2-substituted ynamides and then introduce a trialkylstannyl group at Cα (Scheme 2). In this letter, we will describe the preparation of various α-tributylstannyl β-substituted enamides and preliminary results of subsequent cross-coupling.



R1 ≠ H

Scheme 2. Synthesis of stannylated enamides.

The first step of our approach was therefore the synthesis of various 3-substituted ynamides. Coupling of bromo-alkynes with amides following the Hsung procedure easily affords the expected starting ynamides (Scheme 3).[6]



Scheme 3. Synthesis of 3-substituted ynamides using the Hsung protocol.

All products obtained using this procedure are displayed in Table 1.

As reported in Table 1, numerous ynamides can be obtained with modest to good yields. Different amides can be engaged in such reactions including sulfonamides (entries 1, 9, 14 and 21), oxazolidinones (entries 2–5, 10–11 and 15–18) or even imidazolidinones (entries 7, 12–13, 19–20 and 24) and pyrrolidinone (entry 8). The bromo-alkynes used in the coupling can also range from

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Table 1. Synthesis of 3-substituted ynamides

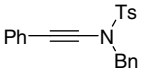
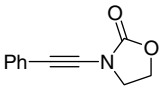
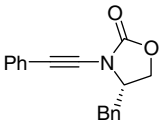
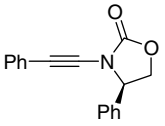
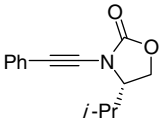
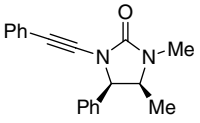
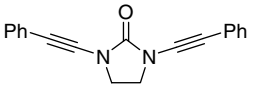
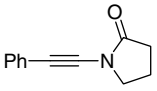
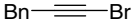
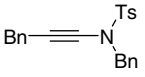
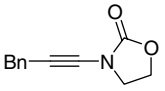
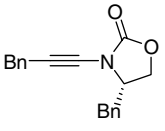
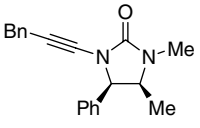
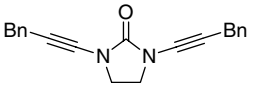
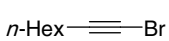
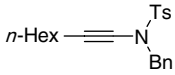
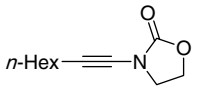
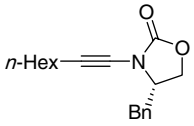
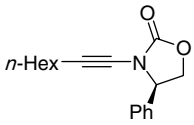
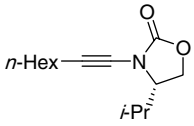
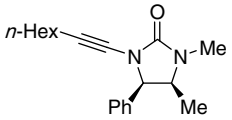
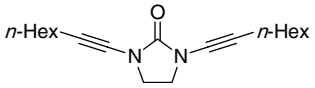
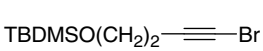
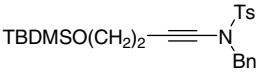
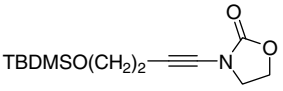
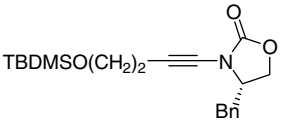
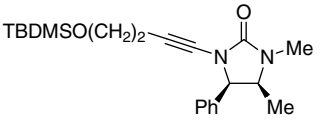
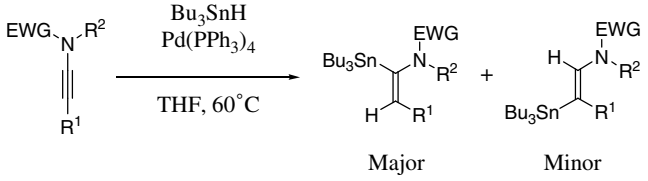
Entry	Amide	Bromo-alkyne	Product	Yield (%)
1	*N*-Benzyltoluenesulfonamide			99
2	Oxazolidinone			62
3	(*S*)-(−)-4-Benzyl-oxazolidinone			35
4	(*R*)-(−)-4-Phenyl-oxazolidinone			75
5	(*S*)-(−)-4-Isopropyl-oxazolidinone			68
6	(4*R*,5*S*)-(−)-1,5-Dimethyl-4-phenylimidazolidinone			82
7	Imidazolidinone			40
8	Pyrrolidinone			38
9	*N*-Benzyltoluenesulfonamide			80
10	Oxazolidinone			58
11	(*S*)-(−)-4-Benzyl-oxazolidinone			33
12	(4*R*,5*S*)-(−)-1,5-Dimethyl-4-phenylimidazolidinone			78
13	Imidazolidinone			30
14	*N*-Benzyltoluenesulfonamide			53
15	Oxazolidinone			65

Table 1 (*continued*)

Entry	Amide	Bromo-alkyne	Product	Yield (%)
16	(*S*)-(−)-4-Benzyl-oxazolidinone			46
17	(*R*)-(−)-4-Phenyl-oxazolidinone			52
18	(*S*)-(−)-4-Isopropyl-oxazolidinone			40
19	(4*R*,5*S*)-(−)-1,5-Dimethyl-4-phenylimidazolidinone			55
20	Imidazolidinone			26
21	*N*-Benzyltoluenesulfonamide			72
22	Oxazolidinone			59
23	(*S*)-(−)-4-Benzyl-oxazolidinone			23
24	(4*R*,5*S*)-(−)-1,5-Dimethyl-4-phenylimidazolidinone			85

aliphatic (entries 14–24) to aromatic (entries 1–8) moieties including benzylic derivatives (entries 9–13). Then, with these ynamides in hand, the next step was the synthesis of the desired stannylated product. As previously described,[4] a mixture of ynamide, Bu_3SnH and $Pd(PPh_3)_4$ was stirred in THF at 60 °C under nitrogen until complete disappearance of the starting ynamide as checked by TLC (usually overnight). The crude mixture was then evaporated to dryness and the ratio of *E*/*Z* compounds was directly assigned by ^1H NMR (Scheme 4).



Scheme 4. Hydrostannation of 3-substituted ynamides.

The results are summarized in Table 2.

It is worth noting that most of the previously synthesized ynamides can be subjected to palladium-catalyzed hydrostannation. This reaction usually proceeds with fair regioselectivities. The lowest regioselectivities are usually obtained with phenyl substituted ynamides (entries 1, 9 and 13). It also appears that the acyclic sulfonamides give a larger amount of β-stannylated enamides (entries 1–4) when compared to carbamates or ureas. The best ratios were obtained with cyclic amides, in this case an intermolecular chelation of the carbonyl oxygen atom to the tin atom could favour the formation of the α-isomer. We should add that, in most cases, no trans addition product could be detected by NMR except for the silylated protected alcohol (entries 4, 8 and 11). Finally, a double hydrostannylation of imidazolidinones bearing two alkyne moieties on the N1 and N3 nitrogen atoms was successful (entries 18–19). This should pave

Table 2. Synthesis of β-substituted α-tributylstannyl enamides

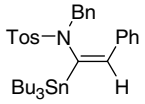
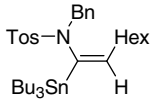
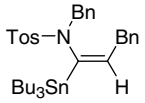
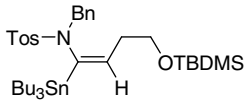
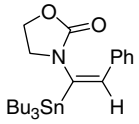
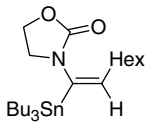
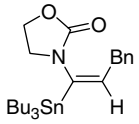
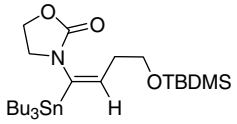
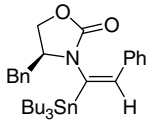
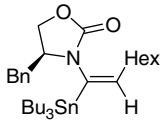
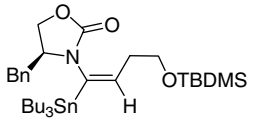
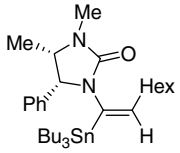
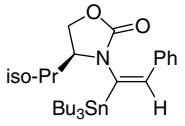
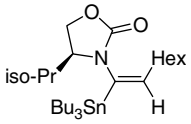
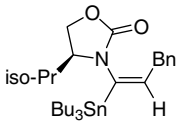
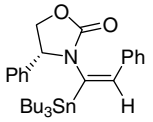
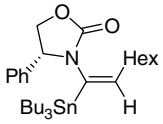
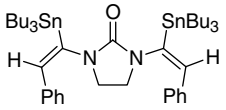
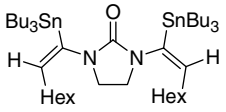
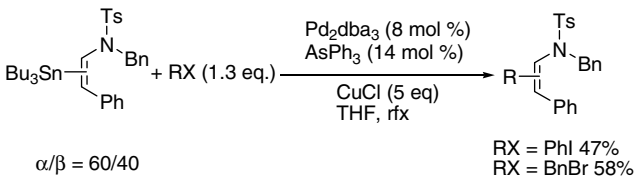
Entry	β-Substituted α-stannyl enamides	Yield (%)	(α/β)[a]
1		53	60/40
2		34	80/20
3		23	87/13
4		22	74/26[b]
5		70	>95/5
6		39	>95/5
7		58	>95/5
8		39	—[c]
9		66	88/12
10		47	>95/5
11		86	93/7[d]
12		56	>95/5
13		62	66/34

Table 2 (*continued*)

Entry	β-Substituted α-stannyl enamides	Yield (%)	(α/β)[a]
14		65	>95/5
15		47	>95/5
16		60	>95/5
17		24	91/9
18		51	96/4
19		80	91/9

[a] Assigned by ^{1}H NMR of the crude mixture.
[b] About 20% of α-trans compound was also observed.
[c] Not determined.
[d] Traces of α-trans compound were also observed (<5%).

the way for the synthesis of a new class of acyclic or cyclic polyureas. We are currently focussing our efforts on the synthesis of these polymers, which could have potential applications for coatings, lubricants or supramolecular architectures. Finally in order to check that these enamides could be involved in cross-coupling reactions to furnish α,β-disubstituted enamides, a mixture of α- and β-tributylstannyl β-phenyl *N*-tosyl *N*-benzyl ynamide was subjected to our previously described conditions[7] (Scheme 5). The reaction proceeded smoothly over 72 hours to afford the expected cross-coupling products with in each reaction 10/15% of the hydrolyzed compound (R = H in Scheme 5). The ratio of α- and β-isomer obtained was consistent with the isomers ratio of the starting material.



Scheme 5. Cross-coupling of a β-phenyl stannylated enamide.

Further experiments are now in progress to expand the scope of this reaction and our results in this field will be reported in due course.

In summary, we report here the first synthesis of β-substituted α-stannyl enamides. Our approach furnishes the expected regioisomer with, in most cases, complete control of the double bond stereochemistry. Finally, first attempts of cross-coupling reaction with one of these stannyl enamides successfully afforded the expected product. This work should compliment the previously described carbometallation of ynamides where trisubstituted or β-disubstituted enamides are obtained.[8]

References and notes

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