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DOI: 10.1039/C8CC04946G

COMMUNICATION

Diastereoselective Synthesis of 1,3-disubstituted Isoindolines and Sultams via Bronsted Acid Catalysis

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

DOI: 10.1039/x0xx00000x

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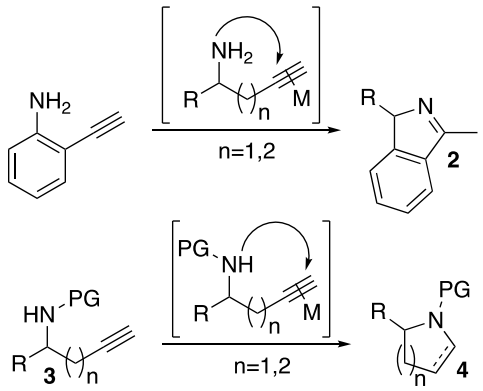
The Bis(trifluoromethane)sulfonimide (Tf_2NH) catalyzed intramolecular hydroamidation of terminal alkynes is reported. The combination of Et_3SiH and Tf_2NH provide cis-1,3-disubstituted isoindolines and sultams in high yield (up to 98%) and high diastereoselectivity (up to 99:1 dr).

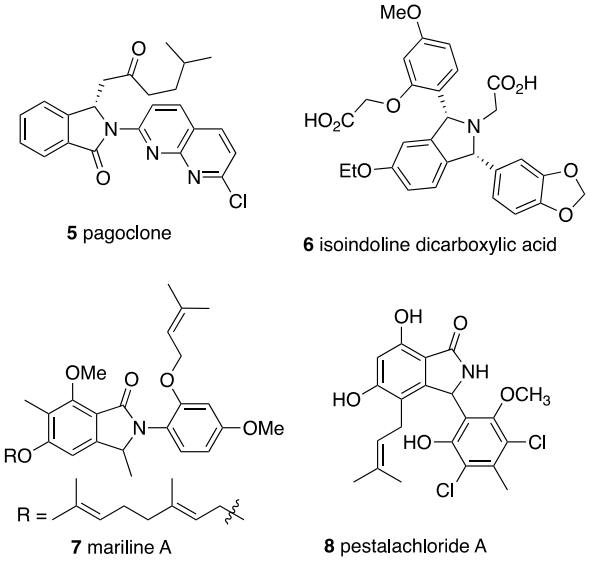
Isoindolines and sultams are important building blocks that are found in a number of biologically active molecules. [1, 2] They have been synthesized by a variety of different bond connections, including carbon-carbon bond and nitrogen-sulfur bond formation. One other approach that has been utilized is via transition metal catalyzed intramolecular hydroamination of



Scheme 1, General hydroamination of alkynes

alkynes. (Scheme 1). Various metals, including rhodium,[3] iridium,[4-6], copper,[7, 8] silver,[9] gold,[10-12] palladium,[13, 14] and ruthenium[15, 16] complexes, have been used to promote such reactions.[17-19] In addition to the metal catalyzed approaches, Shibuya has illustrated that Bronsted acids can effectively catalyze hydroamination.[20-26] Using related conditions we report the formation of both isoindolines and sulfams by Bronstead acid catalyzed intramolecular hydroamidation.

Isoindolines are a common structural motif in a variety of pharmaceuticals and bio-active compounds such as mariline A, petalachloride A, pagoclone and isoindoline dicarboxylic acid (Figure 1).[27-31] Although, there are reported methods to synthesize chiral 1,3-disubstituted isoindolines from hydroamidation of active alkenes (Scheme 2), the asymmetric synthesis of chiral 1,3-disubstituted isoidolines from unactivated unsaturated groups remains underdeveloped.[32-35]



5 pagoclone

6 isoindoline dicarboxylic acid

7 mariline A

8 pestalachloride A

Figure 1

The first example of diastereoselective hydroamidation we report is of terminal alkynes to construct chiral 1,3-disubstituted isoindoline. Initially, copper catalysis with a hydride source, Et_3SiH, at room temperature was examined (Table 1). However, the reaction with terminal alkynes did not proceed (entry 1-2). Increasing the temperature and changing ligands provided exocyclic alkenes (**14**) instead of reduced

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† Footnotes relating to the title and/or authors should appear here.
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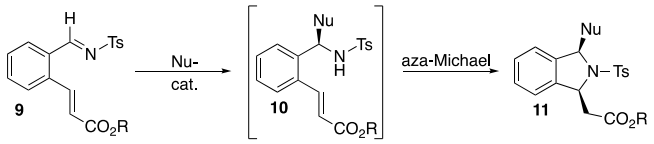
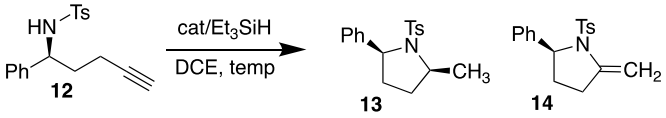


Scheme 2 Cyclication on activated alkenes

products (**13**) (entry 3-4). Attempting acid catalysis with trifluoromethanesulfonic acid (TfOH) resulted in only recovered starting material (entry 5). Using the stronger acid, trifluoromethanesulfonimide (Tf_2NH) resulted in the isolation of chiral cis-1,3-disubstituted pyrrolidine (entry 6). Reaction with 20% Tf_2NH and 2 equivalent Et_3SiH at room temperature gave the 1,3-disubstituted isoindoline in 95% yield and >99:1 diastereoselectivity (entry 7).

Table 1. Reaction Conditions for Cyclization



Entry	cat	ligand	T °C	% Yield 13	14
1	$Cu(OTf)_2$	PPh_3	rt	--	
2	$Cu(OTf)_2$•C_6H_6	PPh_3	rt	--	
3	$CuSO_4$•$5H_2O$	1,10-phenanthroline	80	--	60[b]
4	CuBr	1,10-phenanthroline	80	--	73[b]
5	TfOH	--	50	--	
6	Tf_2NH	--	50	42[c]	--
7	Tf_2NH	--	rt	95[d]	--

[a]Reaction conditions: 0.1 M solution of alkyne (0.15 mmol) in DCE, with 15 mol% metal catalyst or 20 mol% organocatalyst, 2 equiv Et_3SiH, overnight. [b]isolated yield with no reduced product formed. [c]isolated yield of desired product, 1 hour reaction time. [d]isolated yield of desired cis-1,3-disubstituted isoindoline.

When this chemistry is combined with the use of Ellman's *tert*-butanesulfinamide, a chiral immine is obtained (**18**). Addition of Grignard reagent proceeds in high diastereoselectivity (**19**).[36] Attempted cyclization with the the *tert*-butanesulfinamide failed so that group was exchanged for *p*-toluenesulfonamide which upon cyclization provided chiral **22a**. The chiral center set by addition to Ellman's chiral auxillary results in cyclization giving chiral products in high selectivity.

With these optimized conditions the substrate scope was investigated. Aromatic, saturated and unsaturated alkyl groups on R^3-position displayed good to excellent reactivity and excellent diastereoselectivity. Functionality on aromatic ring, electron donating groups (OMe **22g** and **22h**) and electron withdrawing groups (F **22i** and **22j**) exhibited good yields and selectivities (Scheme 4).

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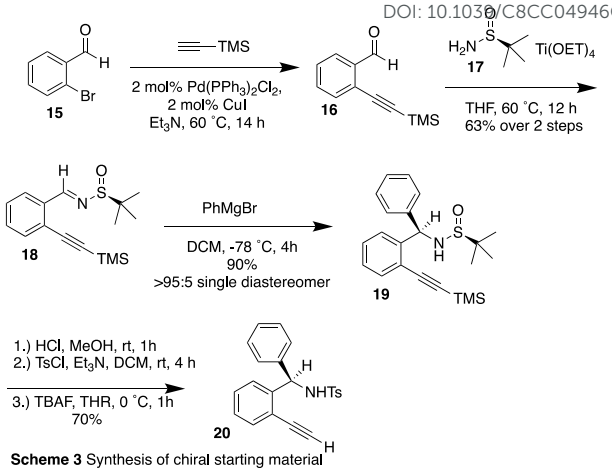
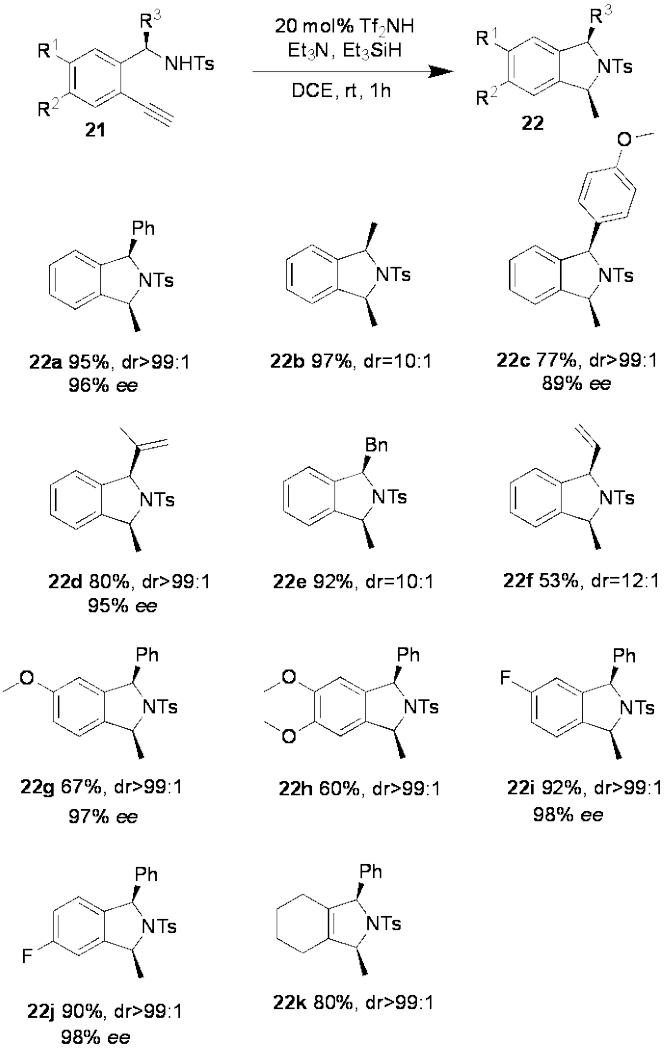


Scheme 3 Synthesis of chiral starting material

Attempts for use other groups on the nitrogen such as carbamates (Boc or Cbz) as well as simple amides did not provide the desired product. The reaction with internal alkynes provided only unreacted starting material.

Positioning the sulfone group at an internal position next the aromatic ring provides sultam products upon cyclization.



Scheme 4. Pyrrolidine Formation

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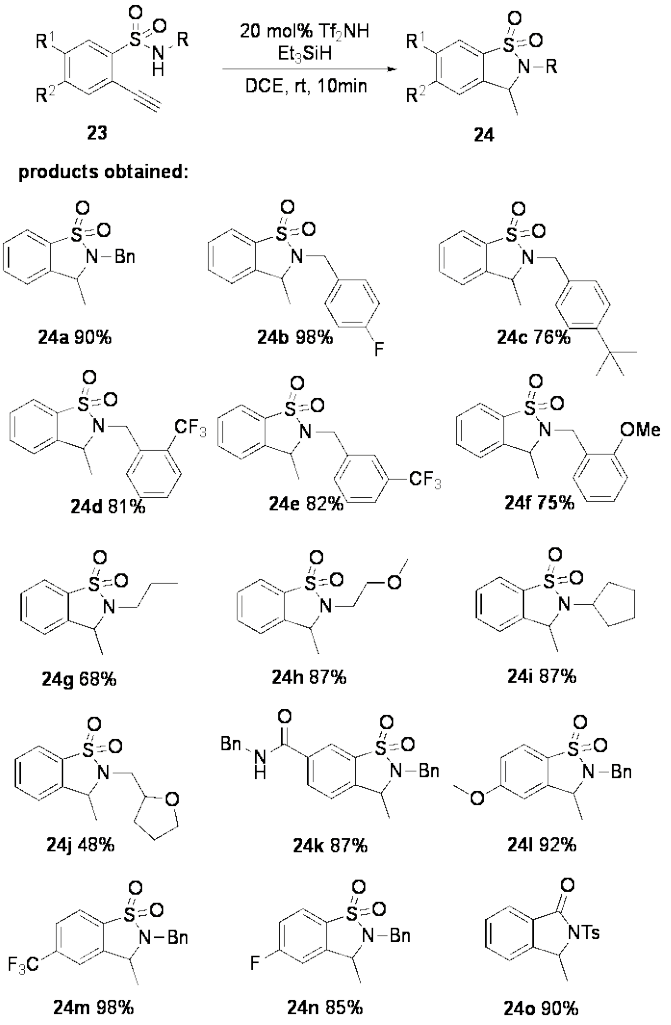
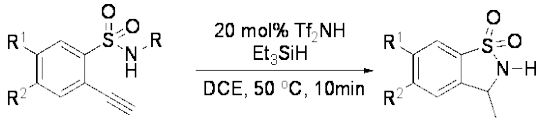
Sultams have been valuable structures in antiviral, anticancer, antimicrobial , antimalarial agents. Using the reaction conditions developed for the synthesis of isoindolines, sultam products were obtained in high yield. Interestingly, this transformation only requires a reaction time of 10 minutes at room temperature. Using these conditions, the substrate scope was investigated. Substrates with benzyl groups and alkyl groups in the R-position, as well as functionality on aromatic ring proceeded in good yield (Scheme 5). All attempts to perform this reaction with simple internal alkynes failed to provide significant product.

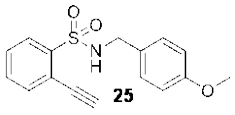
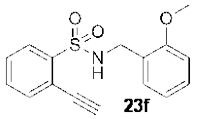
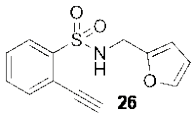
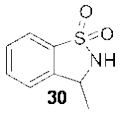
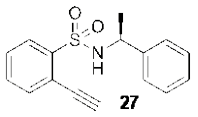
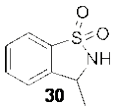
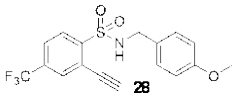
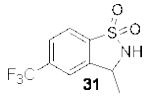
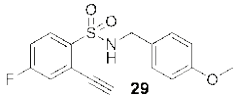
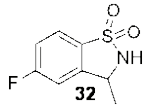


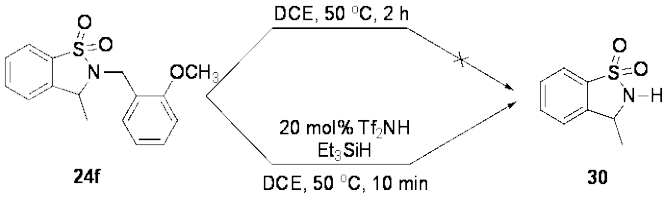
Scheme 5 Synthesis of Sultams

When the reaction was run at 50 °C with substrates that have a electron rich benzyl and furan protected amine, or a group of similar functionality, on the nitrogen the product where that group has been removed, resulting in free sulfonamides, is obtained (Table 2). Presumably this is due to the reactivity of the CH_2 group next to the aromatic ring. To determine how this type of product formed **24f** was heated to 50 °C in dichloroethane (Scheme 6). These conditions did not produce the free sulfonamide **30**. However when isolated **24f** was subjected to the reaction conditions, 20 mol% Tf_2NH and two equivalent Et_3SiH (same conditions as Table 2), free sulfonamide product **30** was obtained. This is consistent with the benzyl group being removed under the reaction conditions after the initial sultam has formed. So by running the reaction at room temperature the product with a protected nitrogen is obtained while running the reaction at 50 ˚C provides the product with a free amine NH. This compliments the observation that the reaction fails with primary sulfonamides.

Table 2. Cyclization with loss of nitrogen group



Entry	SM	product	yield
1			98%[b]
2			67%[b]
3			76%[b]
4			82%[b]
5			96%[b]
6			90%[b]



Scheme 6 Examination of loss of nitrogen protecting group

In summary, we have achieved the catalytic synthesis of chiral cis-1,3-disubstituted isoindolines and sultams through Tf_2NH, Et_3SiH combination approach, by utilizing terminal alkynes as starting materials. This chemistry is currently being developed for the synthesis of biologically active molecules with a SO_2N group representing an amide pharmacophore.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

This work was supported in part by NSF CHE-0953083 and the University of Houston

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36. Stereochemistry of the products was assigned by correlation to previous examples by Ellman.

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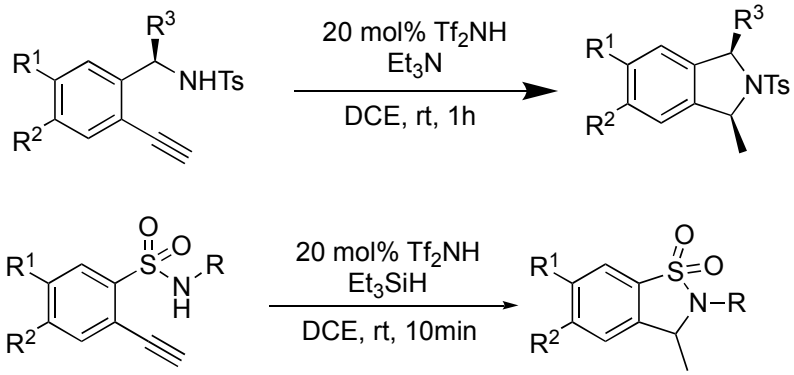

Isoindolines and Sultams formed under mild condictions