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

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## COMMUNICATION

# Diastereoselective Synthesis of 1,3-disubstituted Isoindolines and Sultams via Bronsted Acid Catalysis
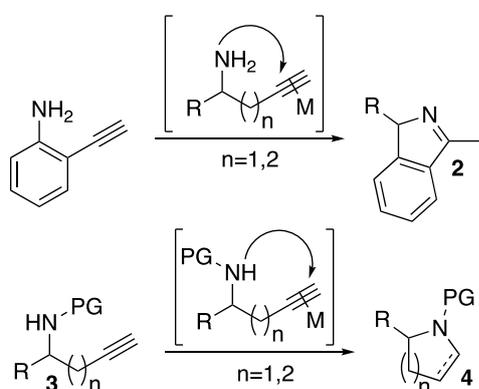
Ye Tao and Scott R. Gilbertson,*[a]

**The Bis(trifluoromethane)sulfonimide (Tf₂NH) catalyzed intramolecular hydroamidation of terminal alkynes is reported. The combination of Et₃SiH and Tf₂NH 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
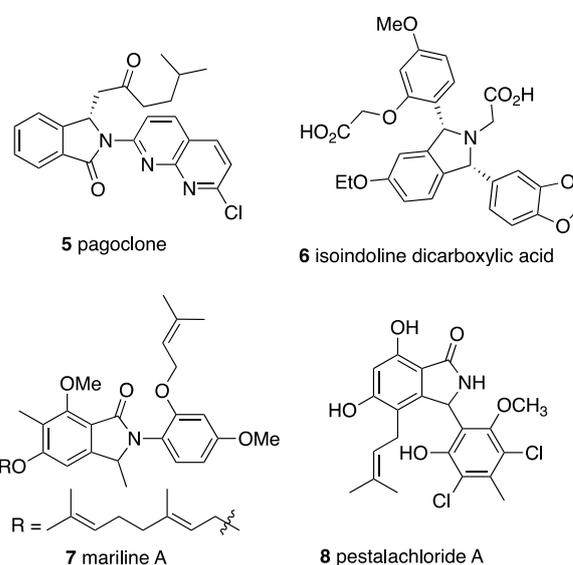
**7** mariline A

**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, Et₃SiH, 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
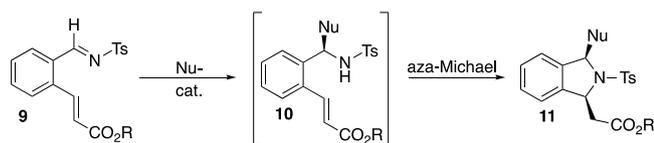
**Scheme 2** Cyclication on activated alkenes

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$_6$H$_6$ | PPh$_3$ | rt | -- | |
| 3 | CuSO$_4$·5H$_2$O | 1,10-phenanthroline | 80 | -- | 60$^b$ |
| 4 | CuBr | 1,10-phenanthroline | 80 | -- | 73$^b$ |
| 5 | TfOH | -- | 50 | -- | |
| 6 | Tf$_2$NH | -- | 50 | 42 $^c$ | -- |
| 7 | Tf$_2$NH | -- | 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
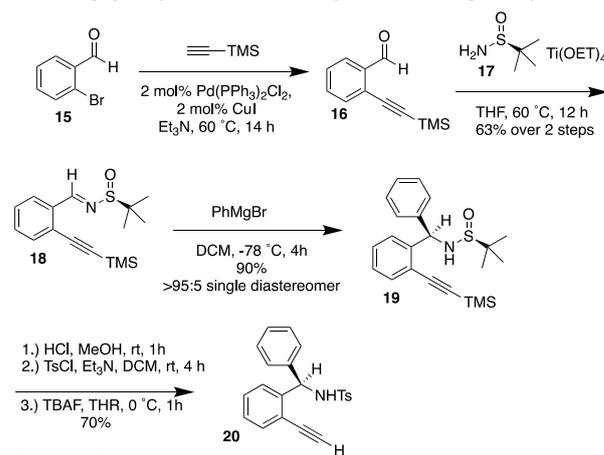




**Scheme 3** Synthesis of chiral starting material

selectivities (Scheme 4).

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.
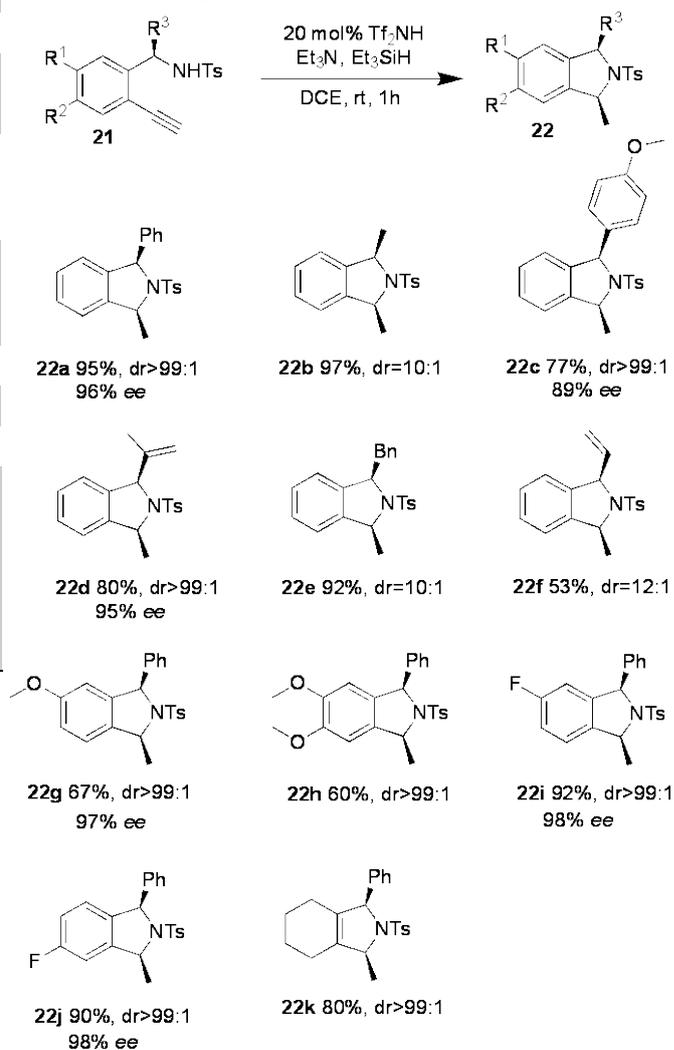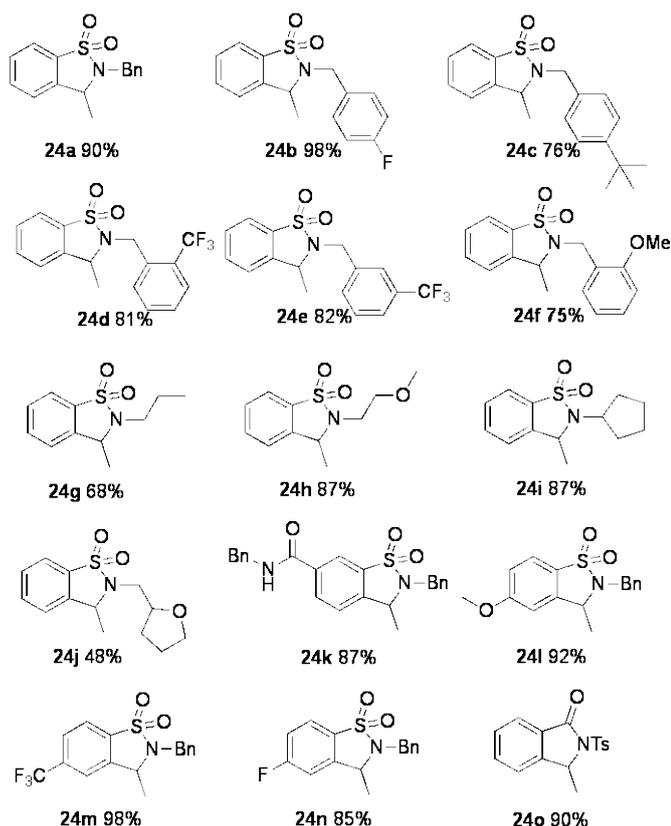


**Scheme 4.** Pyrrolidine Formation

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
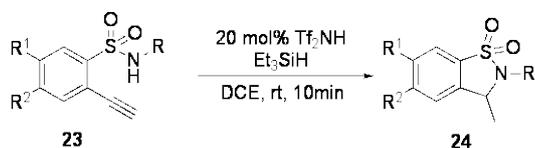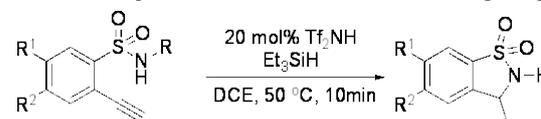


**Scheme 5** Synthesis of Sultams

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.
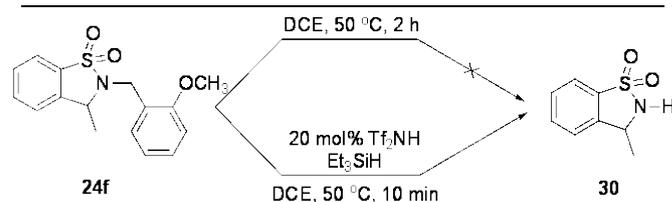
When the reaction was run at 50 ºC with substrates that have a electron rich benzyl and furan protected amine, or a group of similar functionality, on the nitrogen the product where that group has been removed, resulting in free sulfonamides, is obtained (Table 2). Presumably this is due to the reactivity of the $CH_2$ group next to the aromatic ring. To determine how this type of product formed **24f** was heated to 50 ºC 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 | **25** | **30** | 98%[b] |
| 2 | **23f** | **30** | 67%[b] |
| 3 | **26** | **30** | 76%[b] |
| 4 | **27** | **30** | 82%[b] |
| 5 | **28** | **31** | 96%[b] |
| 6 | **29** | **32** | 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

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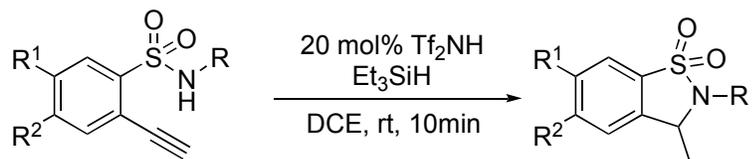
Isoindolines and Sultams formed under mild condictions