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Synthesis of chiral isoindolinones via asymmetric propargylation/lactamization cascade

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ABSTRACT

A Zn-mediated propargylation/lactamization cascade reaction with chiral 2-formylbenzoate derived *N-tert*-butanesulfinyl imines was realized, which provided a practical and efficient method for the synthesis of chiral isoindolinones. High diastereoselectivities (up to 97:3 dr) and good reaction yields were observed for most examined cases.

Chiral isoindolinones are important core structures found in many biologically active compounds (Fig. 1).[1] As a result, significant effort has been devoted to their asymmetric synthesis.[2] Despite the rapid advancement in catalytic approaches,[3–5] methods relying on the utilization of chiral auxiliaries continued to be an attractive strategy due to a myriad of advantages, like the reliability in stereoselectivity control, the easy accessibility of the auxiliary reagents and the possibility of obtaining optical pure products through simple silicon chromatography purification. Several chiral auxiliaries have been used for the diastereoselective synthesis of isoindolinones, including chiral 1-amino-2-methoxymethylpyrrolidines,[6] chiral amino alcohol derivatives,[7] chiral amines and alcohols,[8] and chiral *N-tert*-butanesulfinamide.[9]

Since the seminal work by Ellman and co-workers, chiral *N-tert*-butanesulfinamide auxiliary went through a quick development and proved to be one of the most reliable chiral controller for asymmetric transformation.[10] The addition to chiral 2-formylbenzoate derived *N-tert*-butanesulfinyl imines followed by lactamization can serve as a convenient way to generate 3-substituted isoindolinones, which has been exampled by the previous In-mediated one-pot synthesis of chiral 3-allyl isoindolinone derivatives.[9]

Inspired by recent progresses in Zn-mediated propargylation of *N-tert*-butanesulfinyl imines,[11] we envision a propargylation/lactamization cascade with chiral 2-formylbenzoate derived *N-tert*-butanesulfinyl imines could take place and lead to the easy synthesis of chiral 3-propargyl isoindolinone derivatives, which could also be used as intermediate for the synthesis of more chiral isoindolinone compounds due to the rich transformations associated with propargyl group.[12]

Initially, we tested the proposed propargylation/lactamization cascade with 3-bromopropyne under the reaction conditions developed by Xu and co-workers.[11a] The reaction system was rather complicated and only a small amount of the desired isoindolinone **2** was generated, which may ascribe to the existence of an acidic terminal hydrogen and an active alkyne moiety in 3-bromopropyne (Scheme 1).

Therefore, silyl-protected 3-bromopropyne was used in the next examination (Table 1). To our delight, with 3-(trimethylsilyl) propargyl bromide, the desired product **3a** was produced in 94% yield and 94:6 dr under the reaction conditions reported previously (entry 1).[11b] However, effort to further improve the reaction by solvent screening or adding various Lewis base and acid, a successful tactics in similar allylation reactions,[13] proved fruitless (entries 2–6). Switching the TMS (trimethylsilyl) protect-

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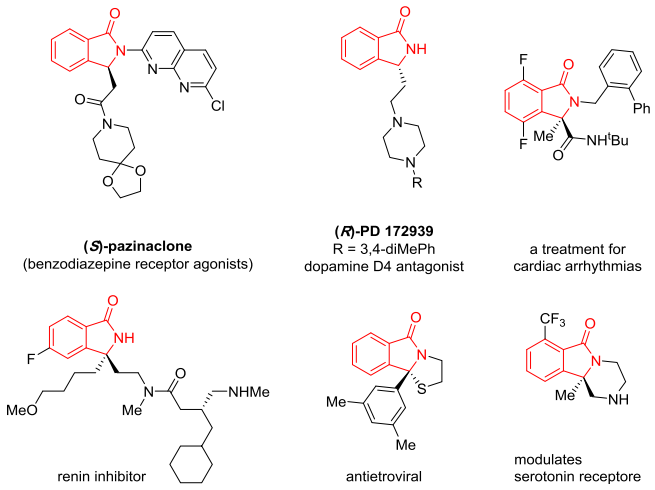
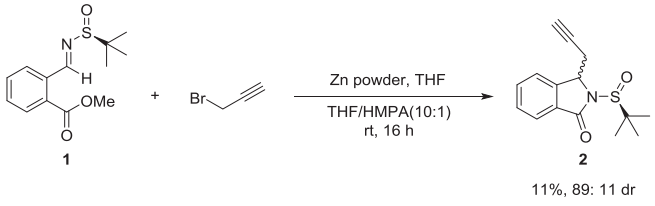


Fig. 1. Selected bio-active chiral isoindolinones.



Scheme 1. Initial attempt with 3-bromopropyne.

ing group to more sterically hindered TBS (*tert*-butyldimethylsilyl) group gave a similar reaction result (entry 7).

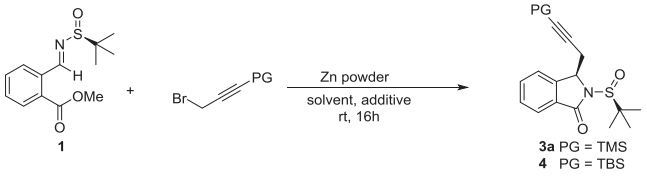
Having established optimal reaction conditions, we began to explore the substrate generality. A variety of 2-formylbenzoate derived *N*-*tert*-butanesulfinyl imines bearing different substituents on the phenyl ring were examined (Table 2). Imines containing either electron-donating or electron-withdrawing groups at C-4 or C-5 position gave excellent reaction yields and high diastereoselectivities (**3c**–**j**). Introduction of a methyl group to the C-3 or C-6 position resulted in decreased reaction yields and diastereoselectivities (**3b** and **3k**), probably due to the steric interaction of between imine (or ester) moiety and the neighboring methyl group. Multi-MeO substituted imines were also suitable substrates, which would be interesting molecules as a mimic of some natural products (**3l**–**n**). Replacing the phenyl ring by a naphthyl group also proceed well albeit in reduced diastereoselectivity (**3o**).

By X-ray crystallography analysis of **3a**, the newly generated C3-stereogenic center was unambiguously determined to be *R*,[14] which may be explained by a six-membered transition-state as depicted in Scheme 2, a similar model proposed previously by Fandrick.[15] Assuming an analogous reaction mechanism, the stereochemistry of other products was tentatively assigned as the same.

As demonstrated in Scheme 3, the *N*-*tert*-butanesulfinyl group in **3a** could be easily cleaved to afford isoindolinone **5** in almost quantitative yield and excellent ee. Deprotection of TMS group by treatment with K_2CO_3 in MeOH gave isoindolinone **6** in excellent yield, but accompanied by a slight racemization. As a versatile intermediate, isoindolinone **6** can undergo a variety of organic transformations, such as click reaction or Sonogashira coupling, to afford new chiral isoindolinone derivatives.

In summary, a propargylation/lactamization cascade with chiral 2-formylbenzoate derived *N*-*tert*-butanesulfinyl imines was realized for the easy preparation of a variety of chiral isoindolinones. The reaction was run under mild reaction conditions, and high diastereoselectivities and good reaction yields were observed for most cases. Further applications of these resulting chiral isoindolinone structures in the synthesis of bioactive molecules are currently underway.

Table 1
Optimization of reaction conditions for propargylation/ lactamization cascade with silyl-protected 3-bromopropyne.



Entry[a]	PG	Solvent	Additive	Yield (%)[b]	dr[c]
1	TMS	THF	none	94	94:6
2	TMS	DMF	none	trace	–
3	TMS	MeCN	none	trace	–
4	TMS	THF	0.1 mL HMPA	63	92:8
5	TMS	THF	0.3 eq $In(OTf)_3$	trace	–
6	TMS	THF	0.3 eq $Mg(OTf)_2$	trace	–
7	TBS	THF	none	91	92:8

[a] Reactions performed using imine **1a** (0.5 mmol), Zn powder (1.0 mmol), and 3-bromo-1-(trimethylsilyl)-1-propyne (1.0 mml) in solvent (2 mL) at room temperature for 16 h.
[b] Yield refers to the isolated major isomer.
[c] Diaterstreoselectivity ratio was determined by ^1H NMR analysis of the crdued product.