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Enantioselective Formation of 3-Substituted Indolinoazepines via Organocatalyzed Conjugate Addition of Indoloazepines to Propargyl Aldehyde

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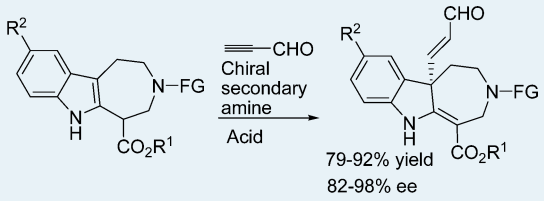
Supporting Information

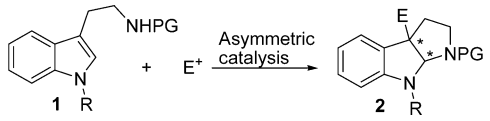
ABSTRACT: An enantioselective Michael addition has been developed to give 3-substituted indolinoazepines by using indoloazepines as nucleophiles and propargyl aldehyde as electrophile under the promotion of a combination of a chiral secondary amine and trichloro acetic acid. By following the optimized protocol, a library of chiral indolinoazepines with a different substitution pattern was obtained in good to excellent yields and excellent enantioselectivities.



KEYWORDS: *organocatalysis, conjugate addition, indoloazepine, propargyl aldehyde, indolinoazepine*

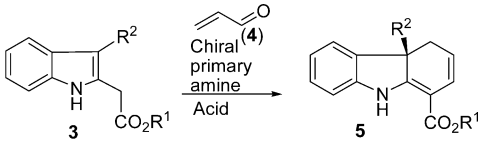
Chiral polycyclic indolines are frequently found among alkaloids and bioactive compounds,[1] and in the past few years, enormous synthetic efforts have been invested in their construction.[2−5] Due to the rich reactivity profile of indoles and ready availability of indole feedstocks,[6] recently C3-substituted indole derivatives were frequently employed as reaction partners in annulation reactions leading to chiral polycyclic indolines by means of metal catalysis and organocatalysis.[3,4] Generally, these annulation reactions were initiated by nucleophilic addition of indolic C3 to electrophiles followed by intramolecular addition of an inbuilt nucleophile to the in situ generated imine or iminium moiety. Taking protected tryptamine as an example, pyrroloindolines with different substituents on C3 were prepared enantioselectively by means of oxidation,[5a] amination,[4i] halogenation,[4l,m] alkylation,[4a−j] or arylation[3e] on this position (Scheme 1). Notably, protection of the indolyl nitrogen was usually required, otherwise further addition of this nitrogen to electrophiles might take place.

Scheme 1. Formation of Pyrroloindolines via Functionalization at C3 of Tryptamine Derivatives



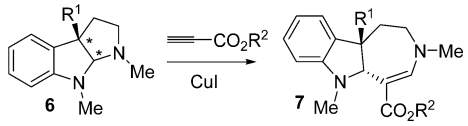
Recently, we have introduced a new strategy for the enantioselective preparation of C2,C3-fused indolines utilizing 2,3-disubstituted indoles bearing an alkoxyl acetyl group at C2. Unlike the fate of the in situ generated imine moiety to be trapped as in the above-mentioned strategy adopted by other groups (Scheme 2),[7] in our case, the imine moiety isomerized into a conjugated enamine, which acts as a nucleophile to furnish an intramolecular cyclization. Notably, protection of the indolyl nitrogen was unnecessary in this strategy, and no further addition of this nitrogen to acrolein was ever observed.

Scheme 2. Organocatalyzed Cycloaddition of 2,3-Disubstitutedindoles with Acrolein



In our opinion, it is reasonable that if an indoloazepine ester was used as the indolic partner in the above reaction, the product would be 3-substituted indolinoazepine ester, which resembles the framework of Hinckdentine and some synthetic bioactive compounds.[8] A literature survey revealed that scant examples for construction of this type of framework have been reported,[9] and the most recent one was Qin and co-workers' synthesis of indolinoazepines by a ring expansion reaction of pyrroloindolines when treated with electron-deficient acetylenes catalyzed by CuI (Scheme 3). Herein we wish to report an organocatalyzed conjugate addition of indoloazepine esters **8** to propargyl aldehyde **9** leading to indolinoazepines **10** with C3 as a quaternary chiral center.

Scheme 3. Qin and Co-Workers' Preparation of Indolinoazepines via Ring Expansion Strategy



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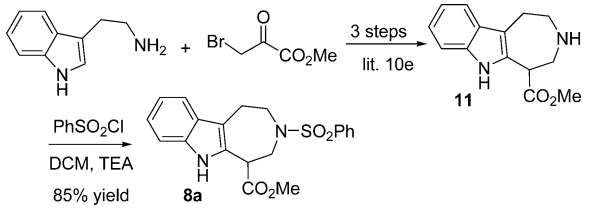
To set the stage for screening of the reaction conditions, substrate **8a** was prepared by *N*-phenylsulfonylation of Kuehne's indoloazepine **11** with phenyl sulphonyl chloride in 85% yield (Scheme 4).[10] However, **11** was obtained from

Scheme 4. Preparation of Indoloazepine Ester 8a

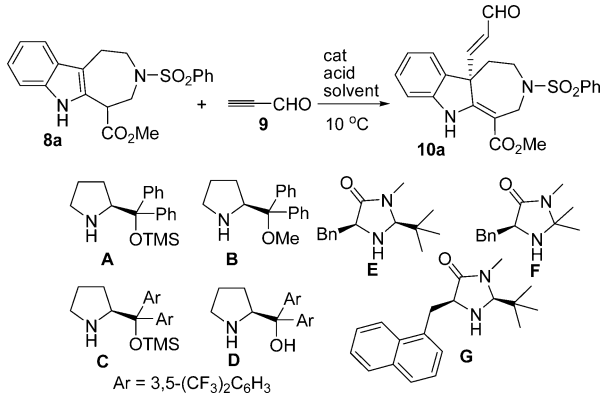


tryptamine and methyl bromopyruvate by using a modification of Kuehne's protocol reported by Li et al.[10e] Following this method, a set of indoloazepine esters with a different substitution pattern were prepared.

To our delight, when propargyl aldehyde **9** was used as the acceptor, a promising preliminary result was obtained after screening of secondary amine catalysts derived from L-proline (Table 1, entries 1–4). Thus, with α,α-diarylprolinol TMS ether (**C**, 20 mol %) as the catalyst,[11] trichloro acetic acid (TCA, 1 equiv) as the additive, and toluene as the solvent, the desired indolinoazepine ester **10a** bearing a 3-oxoprop-1-enyl group at C3 was obtained in a moderate yield of 50% with 27% ee. Fortunately, both the yield and the ee were substantially improved when MacMillan's imidazolidinone catalysts[11] were employed (entries 5–8), and phenylalaline derived catalyst **E** turned out to be the best one in terms of both yield and ee (entry 5).

After evaluation of a number of acidic additives, we found that the performance of TFA in this reaction was comparable to that of TCA (entry 9), although no reaction took place with less acidic additives (entries 10–12). Further optimization through a solvent screening revealed that the reaction was quite solvent dependent (entries 5, 13–20), and toluene proved to be the best (entry 5). Other nonpolar solvents such as DCM, DCE, chloroform, and xylene provided the conjugate adduct in good yield, albeit in slightly lower ee as compared with toluene (entries 13–16). Using ethyl acetate as a solvent, the yield

Table 1. Screening of Reaction Conditions[a]



entry	cat. (20 mol %)	acid (1 equiv)	solvent	yield (%)[b]	ee (%)[c]
1[d]	**A**	TCA	toluene	-	-
2[d]	**B**	TCA	toluene	-	-
3	**C**	TCA	toluene	50	27
4[d]	**D**	TCA	toluene	-	-
5	**E**	TCA	toluene	92	98
6	**F**	TCA	toluene	73	67
7	**G**	TCA	toluene	91	98
8	**E**	TFA	toluene	91	92
9[d]	**E**	BzOH	toluene	-	-
10[d]	**E**	4-CF_3–$C_6H_4CO_2H$	toluene	-	-
11[d]	**E**	2-NO_2–$C_6H_4CO_2H$	toluene	-	-
12[d]	**E**	3,5-$(NO_2)_2C_6H_4CO_2H$	toluene	-	-
13	**E**	TCA	DCM	90	82
14	**E**	TCA	DCE	73	81
15	**E**	TCA	chloroform	95	89
16	**E**	TCA	*o*-xylene	74	93
17	**E**	TCA	EtOAc	20	87
18[d]	**E**	TCA	THF	-	-
19[d]	**E**	TCA	DMF	-	-
20[d]	**E**	TCA	ethanol	-	-
21[e]	**E**	TCA	toluene	60	95

[a]General conditions: **8a** (0.20 mmol), **9** (0.60 mmol), catalyst (20 mol %), and additive (1 equiv) in solvent (5 mL) at 10 °C for 0.5 to 1 h. [b]Yield referred to isolated pure **10a** (completely *E* selective). [c]Enantiomeric excess of **10a** was determined by chiral HPLC analysis. [d]No reaction. [e]The reaction was conducted with 10 mol % **E** and 0.5 equiv TCA.

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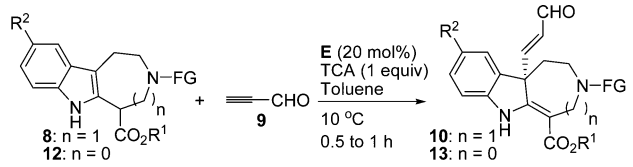
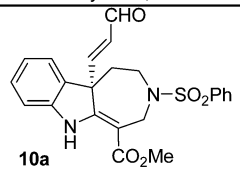
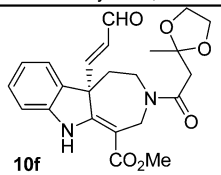
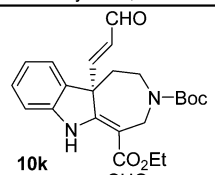
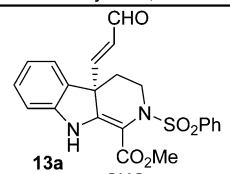
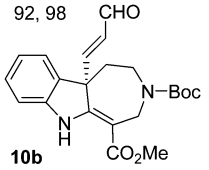
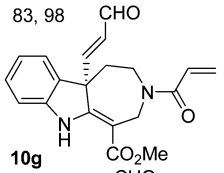
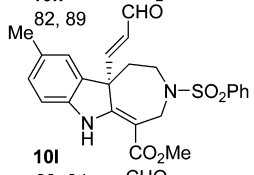
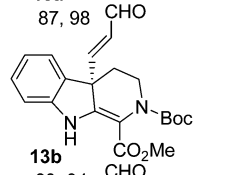
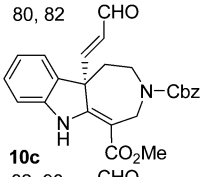
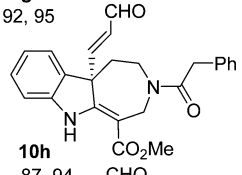
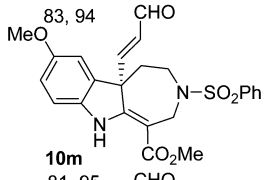
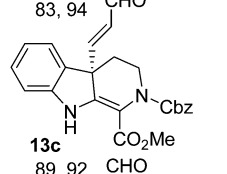
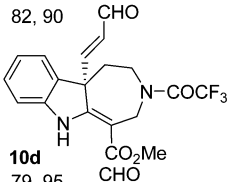
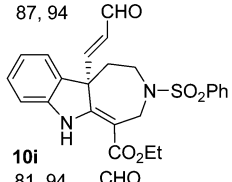
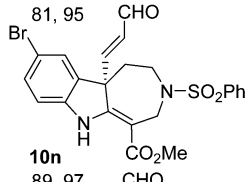
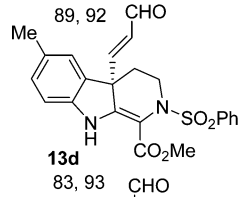
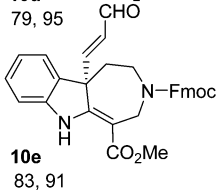
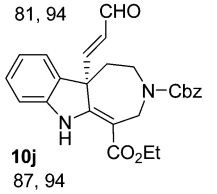
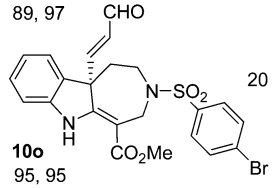
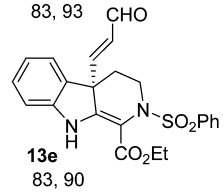
Table 2. Expansion of the Substrate Scope of the Conjuate Addition



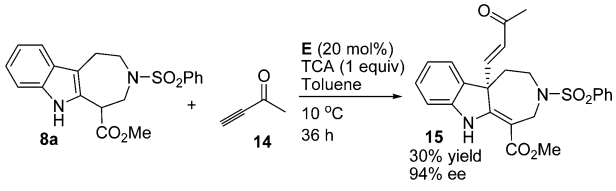
entry	10 yield%, ee%	entry	10 yield%, ee%	entry	10 yield%, ee%	entry	13 yield%, ee%
1	 **10a** 92, 98	6	 **10f** 83, 98	11	 **10k** 82, 89	16	 **13a** 87, 98
2	 **10b** 80, 82	7	 **10g** 92, 95	12	 **10l** 83, 94	17	 **13b** 83, 94
3	 **10c** 82, 90	8	 **10h** 87, 94	13	 **10m** 81, 95	18	 **13c** 89, 92
4	 **10d** 79, 95	9	 **10i** 81, 94	14	 **10n** 89, 97	19	 **13d** 83, 93
5	 **10e** 83, 91	10	 **10j** 87, 94	15	 **10o** 95, 95	20	 **13e** 83, 90

dropped abruptly to 20% (entry 17). While polar solvents such as THF, DMF, and ethanol were all ineffective for this reaction (entries 18−20). Furthermore, it was found that higher level of catalyst loading (20 mol %) and stoichiometric amount of TCA was necessary to secure high conversion, as a combination of 10 mol % of catalyst and substoichiometric amount of TCA resulted in a moderate yield of 60% (entry 21).

On the basis of the optimized reaction conditions (Table 1, entry 5), we expanded the substrate scope of this reaction to diversely substituted indoloazepine esters (Table 2). At first, indoloazepines with different electron-withdrawing protection groups on the azepino nitrogen were tested (entries 1−8). The size of the protection groups exhibited no influence on the results of this reaction as C3-substituted indolinoazepine products were all obtained in good to excellent yields and excellent enantioselectivities. Replacing the methoxyl group in the ester moiety with an ethoxyl group, the reactions proceeded almost equally well (entries 1−3 vs entries 9−11). Furthermore, the electronic nature of the substituent on C5 was found to have little influence on the results of this reaction as substrates with electron-donating or electron-withdrawing substituents provided uniformly high yields and enantioselectivities (entries 12−14). Besides indoloazepines, tetrahydropyridoindoles **12** were also tested in the current research. Delightfully, this type of substrate, with a six-membered ring fused to an indole moiety, also worked well to give the products with excellent yields and ee's (entries 16−20). A sluggish reaction was observed when 3-butyn-2-one **14** was employed to react with **8a** affording **15** in 30% yield and 94% ee (Scheme 5).[12]

The absolute configuration of **10o** (entry 15) was unambiguously determined by single-crystal X-ray diffraction analysis (Figure 1).[13] Presumably, the stereochemistry in the formation of the quaternary stereogenic center could be rationalized by means of the transition state depicted in Figure

Scheme 5. Conjugate Addition of 8a to 15



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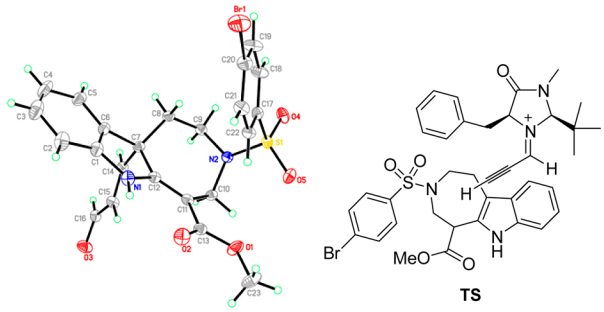
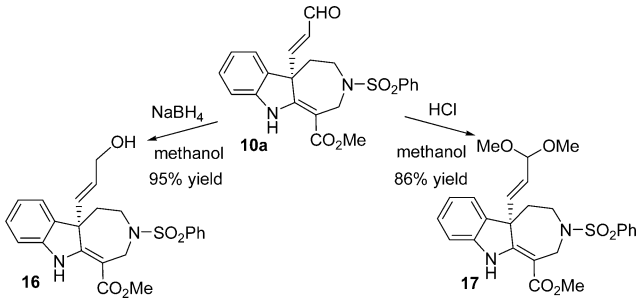


Figure 1. Single-crystal X-ray analysis of **10o** and proposed transition state for the Michael addition.

1 based on the mechanism proposed previously.[11] Specifically, propargyl aldehyde **9** was activated by the MacMillan's catalyst via the formation of an iminium ion, with acetylenic functionality disposed away from the relatively bulky *t*-butyl group; then, the addition of indolic C3 of indoloazepine **8o** to the α,β-unsaturated iminium from less hindered α-side readily took place to afford **10o** with excellent ee. The absolute configuration of other products could be assigned by analogy.

To explore the synthetic potential of the above-mentioned 3-substituted indolinoazepine esters, **10a** was chosen for further manipulation (Scheme 6). Reduction of the aldehyde function

Scheme 6. Further Elaboration of 10a



with $NaBH_4$ in ethanol led to alcohol **16** in high yield. When the aldehyde was treated with HCl in methanol at room temperature for 20 min, acetal **17** was obtained in 88% yield.

In summary, we have developed a new method to prepare chiral indolinoazepine esters bearing an all-carbon quaternary center via conjugate addition of indoloazepine substrates to propargyl aldehyde under the promotion of a combination of MacMillan's imidazolidinone catalyst and TCA. The success of our current system relied on the presence of an ester group on the azepine ring, which stabilized the enamine isomerized from the in situ generated imine function during the addition of indolic C3 to propargyl aldehyde.

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5015496.

General experimental conditions, NMR spectra, and HPLC analysis of the products (PDF).

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Notes

The authors declare no competing financial interest.

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(13) CCDC-1006011 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge CrystallographicData Centre via www.ccdc.cam.ac.uk/data_request/cif.