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Lewis Acid Catalyzed Unprecedented [3 + 2] Cycloaddition Yields 3,3′-Pyrrolidinyldispirooxindoles Containing Four Contiguous Chiral Stereocenters with Two Contiguous Quaternary Spirostereocenters

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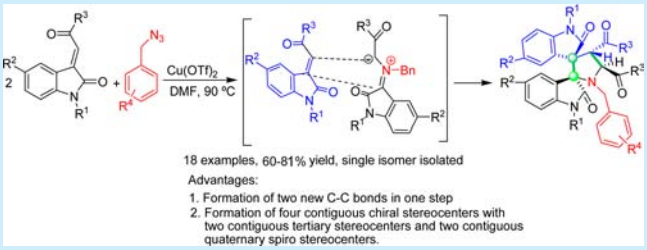
Supporting Information

ABSTRACT: A Lewis acid catalyzed domino reaction cascades through azide−alkene cycloaddition, rearrangement, aziridine ring opening, and azomethine cycloaddition with a parent dipolarophile, resulting in 3,3′-pyrrolidinyldispirooxindoles containing four contiguous chiral stereocenters with two contiguous quaternary spirostereocenters.

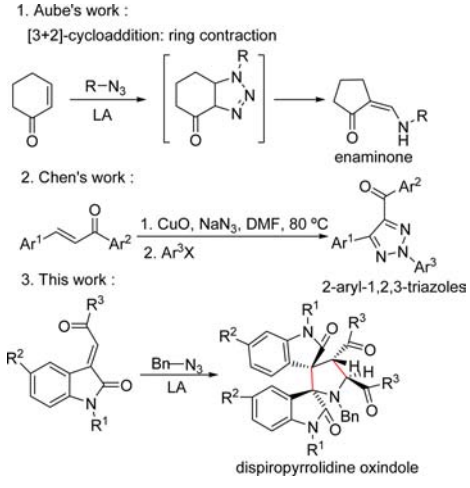


The discovery of click chemistry, particularly, cycloaddition of azide with alkenes, has led to the development of new methodologies for *in situ* generation of azomethine ylides.[1] Herein, we report a one-pot protocol that, to the best of our knowledge, effectuates the unprecedented cycloaddition of azomethine ylides, generated *in situ* through a cascade of azide−alkene 1,3-dipolar cycloaddition reaction sequence, with the parent electron-deficient alkene. The constitution of the cycloadducts obtained reveals the single-step construction of densely functionalized 3,3′-pyrrolidinyldispirooxindoles containing four contiguous chiral stereocenters including two quaternary spirostereocenters, providing extraordinary levels of stereo control.

Spirooxindole structural motif is common to a range of natural products and bioactive compounds.[2−5] Naturally occurring and synthetically important biologically active 3,3′-pyrrolidinylspirooxindoles include horsifiline,[6] spirotryprostatin A, elacomine,[7] MI-219,[3d] Schreiber's lead compound,[2a] and coerulescine.[8] Owing to the significance of 3,3′-pyrrolidinyl spirooxindole scaffolds, extensive efforts have been made for the efficient synthesis of these heterocycles.[9,10] Despite the presence of various methodologies, organo catalytic synthesis of 3,3′-pyrrolidinyl spirooxindoles through [3 + 2] cycloaddition of azomethine ylides with methylene indolinones seems very attractive.[11] However, synthesis of 3,3′-pyrrolidinylspirooxindole scaffolds containing contiguous multiple stereogeniccenters with asymmetric all-carbon quaternary stereocenters remains as a challenging criterion to synthetic chemists. Single-step construction of pyrrolidines containing multiple stereocenters is very rare.[12] 1,3-Dipolar cycloaddition of azomethine ylides with activated alkenes offers a straightforward one-pot method for the efficient construction of highly functionalized pyrrolidine structures.[10d−g,13]

Rearrangements related to azides have played an extensive role in the preparation of nitrogen heterocyclic compounds.[14] Aubé et al. have reported that under TMSOTf-catalyzed conditions, the 1,3-dipolar cycloaddition of benzyl azide with six-membered α,β-unsaturated ketones leads to ring-contraction and the formation of amino enones (Scheme 1).[15a] This interesting

Scheme 1. Tandem [3 + 2] Cycloaddition/Rearrangement



cycloaddition−rearrangement−ring contraction has also been observed in intramolecular [3 + 2] cycloaddition reactions.[15b] However, such a rearrangement−ring contraction has not been observed by Chen et al. in their CuO-catalyzed oxidative cycloaddition of azide with α,β-unsaturated carbonyl compounds that results in the formation of 2-aryl-substituted 1,2,3-triazoles.[16] Further, thermal decomposition of 1,2,3-triazolines provides aziridines which under Lewis acid catalyzed conditions lead to azomethine ylides useful for the construction of

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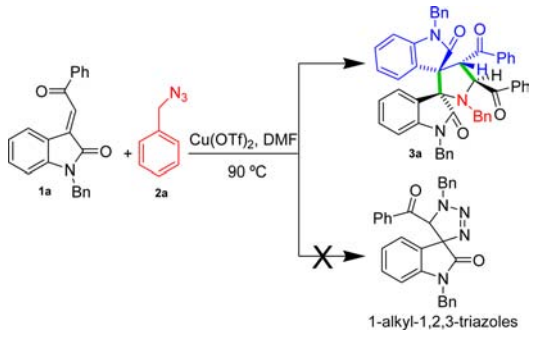
pyrrolidine scaffolds.[17] With these reports in mind, we performed the Lewis acid catalyzed cycloaddition using 1 equiv of benzyl azide, 1 equiv of dipolarophile, (*E*)-1-benzyl-3-(2-oxo-2-phenylethylidene)indolin-2-one, and 2 mol % of $Cu(OTf)_2$ in DMF at 90 °C. Although the starting materials were consumed within 4 h, the appearance of several new spots in TLC prompted us to continue heating until the completion of the reaction. The single product formed after ~12 h was separated using silica gel column chromatography to obtain **3a** in only 32% yield, which was improved further after optimizing the reaction condition and stoichiometry of the reactants.

^{1}H NMR spectroscopic analysis of the product **3a**, revealed the presence of two-doublets at δ 3.50 ppm and δ 5.58 ppm with identical coupling constant values (J = 14.4 Hz) clearly indicating the presence of two vicinal protons, unexpected from a [3 + 2] cycloaddition product. In the ^{13}C NMR spectrum of **3a**, we observed two benzoyl carbonyl peaks at δ 197.4 ppm and δ 198.8 ppm as well as two oxindole carbonyl peaks at δ 175.1 ppm and δ 177.1 ppm, indicating the presence of two phenacylidene-2-indolinone moieties (Scheme 2, **3a**). Interestingly, the single-

Scheme 2. Lewis Acid Catalyzed [3 + 2] Cycloaddition Reaction



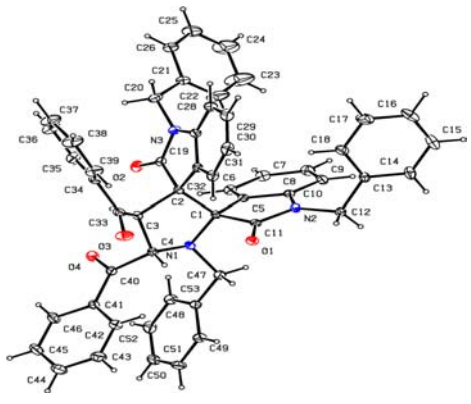


Figure 1. ORTEP diagram of compound **3a**.

crystal X-ray diffraction data (Figure 1) conformed with isomer A (Figure 2) and suggested the formation of azomethine ylide intermediate. It is imperative to note that four chiral centers with two quaternary spirostereocenters are generated in excellent selectivities and high yield, under the reaction conditions described in this procedure, in contrast to the other dispiropyrrolidinyloxindoles obtained from [3 + 2] cycloaddition of azomethine ylides in our laboratory.[18]

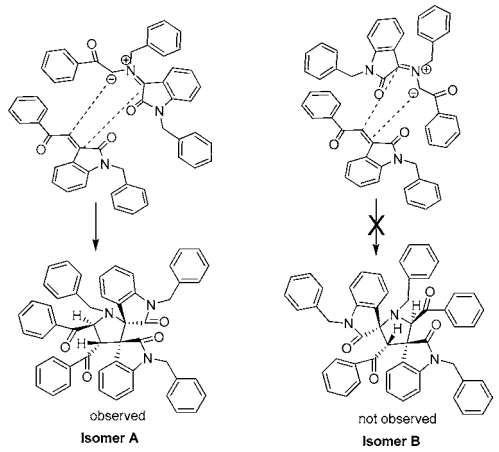
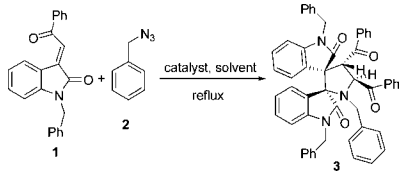


Figure 2. Possible mode of [3 + 2] cycloaddition.

Having identified the unprecedented formation of 3,3′-pyrrolidinyldispirooxindole **3a**, we set out to increase the yield of the reaction by using 2 equiv of (*E*)-1-benzyl-3-(2-oxo-2-phenylethylidene)indolin-2-one and 1 equiv of benzyl azide in the presence of various Lewis acid catalysts (2 mol %) in different solvents and at various temperatures. Among the different catalysts used, $Cu(OTf)_2$ gave good yields in DMF at 90 °C (Table 1). A further increase in the amount of catalyst

Table 1. Optimization of Reaction Conditions



entry	catalyst (mol %)[a]	solvent	temp (°C)	time (h)	yield[b] (%)
1	none	DMF	90	12.0	none
2	$Cu(OAc)_2$	DMSO	90	8.0	trace
3	$Cu(OAc)_2$	DMF	90	16.0	45
4	$CuSO_4$	DMF	90	8.5	38
5	$CuCl_2$	DMF	90	6.2	60
6	CuO	DMF	90	7.2	67
7	$Cu(OTf)_2$	DMSO	90	7.0	65
8	$Cu(OTf)_2$	toluene	95	8.0	55
9	$Cu(OTf)_2$	*o*-xylene	100	8.0	57
10	$Cu(OTf)_2$	DMF	rt	16.0	none
11	$Cu(OTf)_2$	DMF	50	8.2	none
12	$Cu(OTf)_2$	DMF	60	15.0	none
13	$Cu(OTf)_2$	DMF	90	6.2	70
14[c]	**$Cu(OTf)_2$**	**DMF**	**90**	**8.0**	**81**
15	$Sc(OTf)_3$	DMF	80	8.5	35
16	$Bi(OTf)_3$	DMF	90	9.0	42
17	$In(OTf)_3$	DMF	90	8.0	40

[a]Unless otherwise noted, 2 equiv of phenacylidinone, 1 equiv of benzyl azide, and 2 mol % of catalyst were used. [b]Isolated yields after column chromatography. [c]5 mol % of catalyst was used.

[$Cu(OTf)_2$, 5 mol %] showed a remarkable improvement in the yield of the reaction (Table 1, entry 14). No apparent product was observed either in the absence of a catalyst or when the reaction was carried out at room temperature.

After optimizing the reaction conditions, the substrate scope was screened by changing the substituents on the dipolarophile

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1. Good yields were obtained in almost all cases regardless of the electronic nature, bulkiness, or the position of the substituents on the dispirooxindole structure (Table 2). The formation of

Table 2. Substrate Scope[a]

entry	R^1	R^2	Ar	product	yield[b] (%)
1	Bn	H	Ph	**3a**	81
2	Bn	F	Ph	**3b**	74
3	Bn	H	4-biphenyl	**3c**	78
4	Bn	I	Ph	**3d**	76
5	Me	H	Ph	**3e**	74
6	Me	H	4-ClC_6H_4	**3f**	72
7	Me	H	4-BrC_6H_4	**3g**	69
8	Me	H	2-naphthyl	**3h**	62
9	Me	H	4-biphenyl	**3i**	60
10	allyl	H	Ph	**3j**	63
11	allyl	Cl	Ph	**3k**	60
12	allyl	Br	Ph	**3l**	62

[a]All reactions were carried out with 2 equiv of dipolarophile, 1 equiv of benzyl azide, and 5 mol % of $Cu(OTf)_2$ in 5 mL of DMF at 90 °C. [b]Isolated yield after column chromatography.

azomethine ylide and the *trans* stereochemistry of the vicinal protons in the newly formed 3,3′-pyrrolidinyl ring indicated that the reaction proceeded via a stepwise pathway. The generality of this reaction was further explored by using (*E*)-alkyl 2-(1-alkyl-2-oxoindolin-3-ylidene)acetate as dipolarophile. As expected, the reaction occurred smoothly under the optimized reaction conditions and provided the cycloadducts **5a**–**f** in good yields (Table 3).

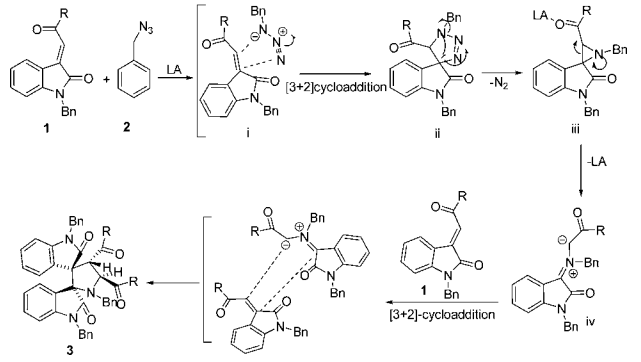
Table 3. Substrate Scope[a]

entry	R^1	R^2	R^3	R^4	product	yield[b] (%)
1	Bn	H	Et	H	**5a**	80
2	Bn	H	Me	H	**5b**	76
3	Me	H	Et	H	**5c**	78
4	Me	H	Me	H	**5d**	74
5	Me	H	Me	4-CN	**5e**	68
6	Me	H	Me	4-*tert*-butyl	**5f**	60

[a]All reactions were carried out with 2 equiv of dipolarophile, 1 equiv of benzyl azide, and 5 mol % of $Cu(OTf)_2$ in 5 mL DMF at 90 °C. [b]Isolated yield after column chromatography.

Based on spectroscopic and X-ray diffraction studies on product **3a**, a plausible mechanism for the formation of compounds **3a**–**l** and **5a**–**f** as shown in Scheme 3 is proposed. Our proposition is that the Lewis acid catalyzed reaction initially undergoes the formal [3 + 2] cycloaddition of benzyl azide with the dipolarophile **1**, resulting in the formation of [1,2,3]-

Scheme 3. Plausible Mechanism



triazolines. The thermal or acid-promoted decomposition of triazolines could then lead to the formation of strained aziridines, which in the presence of a Lewis acid could have transformed into azomethine ylide through carbon–carbon bond cleavage of aziridines. The azomethine ylide thus generated *in situ* might then undergo regioselective [3 + 2] cycloaddition with the unreacted dipolarophile **1**, yielding one of the two possible isomers of **3**. It appears that the *E*-isomer of dipolarophile and the *Z*-isomer of the azomethine ylide take part in the second [3 + 2] cyloaddition resulting in the formation of **3** with the pyrrolidine protons 4H and 5H in a *trans* orientation (Scheme 3).

In summary, Lewis acid catalyzed azide–alkene cycloaddition leading to the highly regio- and stereoselective formation of densely functionalized dispiropyrrolidine derivatives is reported. The unique advantages of this one-step methodology are (1) the formation of two new C–C bonds in a single step, (2) generation of four contiguous chiral stereocenters with two contiguous spiro-quaternary stereocenters, and (3) regio- and diastereoselective formation of highly functionalized single isomer. We believe that the method described in this report would enable further generation of biologically important highly functionalized dispiro 3,3′-pyrrolidinyloxindoles with high stereoselectivity in good yields.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedure, spectroscopic characterization of the compounds, and X-ray crystal data of compound **3a** (CCDC 980987).This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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