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Lewis Acid Catalyzed Atom-Economic Synthesis of C2-Substituted Indoles from *o*-Amido Alkynols

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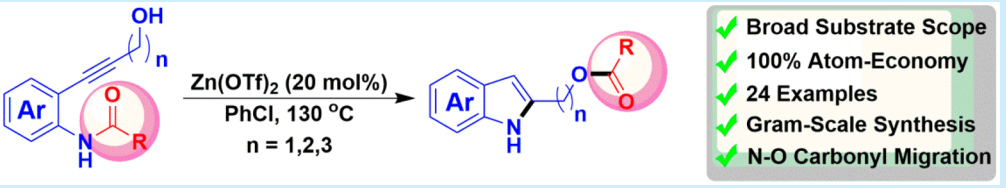
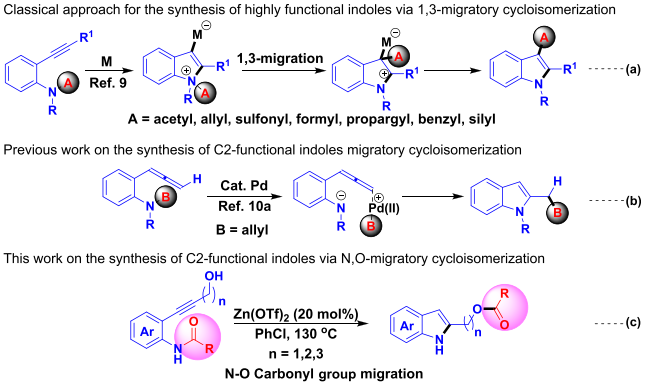


ABSTRACT: Herein we have disclosed a $Zn(OTf)_2$ catalyzed synthesis of C2-alkyl substituted indole derivatives via unprecedented carbonyl group migration from *o*-amido alkynols. The key features of this protocol involve N,O-carbonyl group migration, broad substrate scope with varied functionality tolerance, moderate to good yields, and 100% atom economy. The crossover experiments proved that the migration is happening via an intramolecular pathway.

Indole derivatives, one of the privileged classes of *aza*-heterocycles, are prevalent in a variety of engrossing compounds such as natural products, medicinal agents, alkaloids, and bioactive molecules exhibiting a wide range of pharmacological activities like anticancer, antiviral, antibacterial, etc.[1] Hence a variety of synthetic methodologies have been developed including some of the classical name reactions such as Fischer indole synthesis,[2] Bischler indole synthesis,[3] Sundberg indole synthesis,[4] Larock indole synthesis,[5] Bartoli indole synthesis,[6] Fukuyama indole synthesis,[7] etc. Although among them, the synthesis of only C2-substituted indoles is considered as one of the toughest routes yet interesting due to the poor nucleophilic nature of the C2 position,[1b,8] several groups attempted the classical strategy of 5-*endo*-dig cyclization of *o*-alkynyl aniline/anilide derivatives under transition-metal (Pd, Rh, Ru, Ag)/Lewis acid catalysis.[9] The key steps for this strategy involves activation of alkyne by π-acidic metal catalysts followed by protodemetalation of the cyclized intermediate.[9f]

Furthermore, transition-metal catalyzed migratory cycloisomerization is one of the most powerful and effective approaches in synthetic chemistry. This approach utilizes the readily accessible starting materials for the mild and selective synthesis of densely functionalized heterocyclic scaffolds with 1,*n*-migration of the functional groups from a heteroatom (N, O, S) disclosing 100% atom economy.[10] These groups include acyl/formyl,[10c,11] sulfonyl,[12] allyl,[10a,12b,13] propargyl,[14] etc. which have been successfully implemented to synthesize highly functional indole derivatives via 1,3-migration (Scheme 1a). Recently, Arisawa et al. demonstrated Pd-catalyzed migratory cycloisomerization of *N*-allyl-*o*-allenyl aniline derivatives to give exclusively C2-functional indoles (Scheme 1b).[10a] However, to the best of our knowledge, there is no any report on the synthesis of C2-substituted N-unprotected indoles from *o*-amido alkynols via N,O-carbonyl group migration.

Scheme 1. Indole Synthesis *via* Migratory Cycloisomerization



On the other hand, alkynols are well-known important structural precursors for the construction of various hetero-/carbocycles via *endo* or *exo* mode of cycloisomerization with varied reaction sequences based on the suitable substrates and reaction conditions.[15] Recently our group also contributed in the synthesis of different *O*-heterocycles by using *o*-alkoxy alkynols as the starting precursor under Lewis/Brønsted acidic

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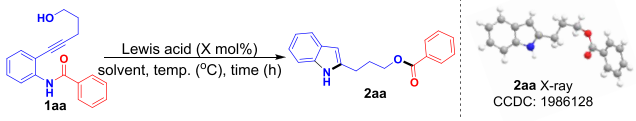
conditions.[16] Hence by considering the importance of migratory cycloisomerization and our continuous research interest in Lewis acid mediated reactions,[16a,17] we have represented Lewis acid catalyzed synthesis of C2-alkyl substituted indoles via unprecedented carbonyl group migration with an atom economic approach (Scheme 1c).

The preliminary optimization began by using *N*-(2-(5-hydroxypent-1-yn-1-yl)phenyl)benzamide (**1aa**) as a model substrate with 20 mol % of $Zn(OTf)_2$ and chlorobenzene as solvent at reflux temperature for 14 h. To our surprise, 3-(1*H*-indol-2-yl)propyl benzoate (**2aa**) was obtained in 74% yield via intramolecular cyclization and migration (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



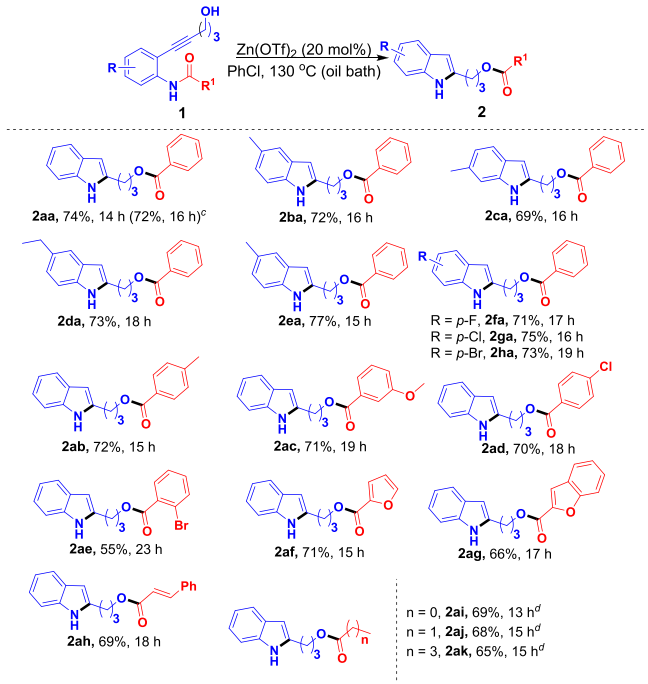
entry	Lewis acid (*X* mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	**$Zn(OTf)_2$ (20)**	**PhCl**[c]	**130**	**14**	**74**
2	$Fe(OTf)_2$ (20)	PhCl	130	14	66
3	$Cu(OTf)_2$ (20)	PhCl	130	14	trace
4	$In(OTf)_3$ (20)	PhCl	130	14	55
5	AgOTf (20)	PhCl	130	16	48
6	$Cu(OAc)_2$ (20)	PhCl	130	19	0
7	$CuBr_2$ (20)	PhCl	130	14	0
8	$CuCl_2$ (20)	PhCl	130	14	trace
9	CuI_2 (20)	PhCl	130	14	~15
10	$InCl_3$ (20)	PhCl	130	14	trace
11	$FeCl_3$ (20)	PhCl	130	10	0
12	ZnI_2 (20)	PhCl	130	14	62
13	BF_3–Et_2O (20)	PhCl	130	14	0
14[d]	TfOH (20)	PhCl	130	12	0
15	$Zn(OTf)_2$ (10)	PhCl	130	14	63
16	$Zn(OTf)_2$ (40)	PhCl	130	14	73
17	$Zn(OTf)_2$ (20)	Toluene	110	14	55
18	$Zn(OTf)_2$ (20)	Xylene	130	14	58
19	$Zn(OTf)_2$ (20)	Trifluorotoluene	100	14	25
20	$Zn(OTf)_2$ (20)	1,2-DCE[e]	80	18	trace
21	$Zn(OTf)_2$ (20)	THF[f]	70	18	~18
22	$Zn(OTf)_2$ (20)	1,4-dioxane	100	15	30
23	$Zn(OTf)_2$ (20)	DMF[g]	130	12	45
24	$Zn(OTf)_2$ (20)	DMSO[h]	130	12	40

[a]All reactions were carried out using **1aa** (0.4 mmol) and Lewis acid (*X* mol %) in the solvent (1.5 mL) at the indicated time and temperature (oil bath) in the sealed tube. The entry in bold (entry 1) highlights the optimized reaction conditions. [b]Isolated yields. [c]PhCl = chlorobenzene. [d]The reaction was carried out with increasing temperatures starting from rt to 60 °C to 90 °C to 130 °C. [e]1,2-DCE = 1,2-dichloroethane. [f]THF = tetrahydrofuran. [g]DMF = *N*,*N*-dimethylformamide. [h]DMSO = dimethyl sulfoxide.

The structure of compound **2aa** was unambiguously confirmed by X-ray analysis (CCDC 1986128). Further, we have carried out the reaction with other metal triflates; however, none of them improved the yield of **2aa** (Table 1, entries 2–5). The reaction with various copper(II) salts, metal halides, and BF_3–Et_2O failed to give the desired compound except for ZnI_2 (Table 1, entries 6–13). To confirm the role of $Zn(OTf)_2$, we carried out the reaction with 20 mol % of TfOH at elevated temperatures (Table 1, entry 14). However, we did not observe the desired product. Later, the catalyst loading was screened (Table 1, entries 15–16) and it was confirmed that 20 mol % of $Zn(OTf)_2$ gave the maximum yield of **2aa** (74%). Finally, the screening of solvents at refluxing temperatures (Table 1, entries 17–24) revealed that chlorobenzene gave the maximum yield of **2aa** (Table 1, entry 1).

With the optimized conditions in hand, an array of *o*-amido pentynols **1** were used for the Lewis acid catalyzed indole synthesis (Scheme 2). Initially the scope was carried out with

Scheme 2. Scope of *o*-Amido 4-Pentyn-1-ols[a,b]



[a]All reactions were carried out using **1** (0.4 mmol) and $Zn(OTf)_2$ (20 mol %) in chlorobenzene (1.5 mL) at 130 °C (oil bath) in the sealed tube. [b]Isolated yields. [c]Reaction carried out at 1.0 mmol scale. [d]30 mol % of $Zn(OTf)_2$ was used.

electron-donating as well as electron-withdrawing substituents attached to R like *p*-Me (**1ba**), *m*-Me (**1ca**), *p*-Et (**1da**), 3,4-diMe (**1ea**), *p*-F (**1fa**), *p*-Cl (**1ga**), and *p*-Br (**1ha**), to give the desired compounds **2ba**–**2ha** in 69–77% yields. Next, the scope of amide derivatives (R^1-group) was investigated with substitutions like *p*-Me-Ph (**1ab**), *m*-OMe-Ph (**1ac**), *p*-Cl-Ph (**1ad**), and *o*-Br-Ph (**1ae**) which afforded the indole derivatives **2ab**–**2ae** in 55–72% yields. Replacing aromatic amides with heteroaromatic amides (**1af**–**1ag**) and cinnamamide (**1ah**) also gave the desired products **2af**–**2ah** in 66–71% yields. Finally the scope was broadened to aliphatic derivatives (**1ai**–**1ak**), and to our delight, the protocol worked smoothly giving products **2ai**–**2ak** in 65–69% yields.

In light of the success with pentynol derivatives, we explored the scope with different chain lengths of alkynol such as 3-butyn-1-ol (**3**) and propargyl alcohol (**4**) under standard reaction conditions (Scheme 3). Surprisingly, the reactions underwent smooth conversion with electron-donating and -withdrawing groups at either side of the substrates (**3aa**, **3ba**, **3fa**, **3ad**, **4aa**–**4ba**, **4ab**) furnishing the desired products **5ba**, **5ad**, **6aa**–**6ba**, **6ab** in 60–68% yields, except for the compound **5aa** which resulted in inseparable spots observed

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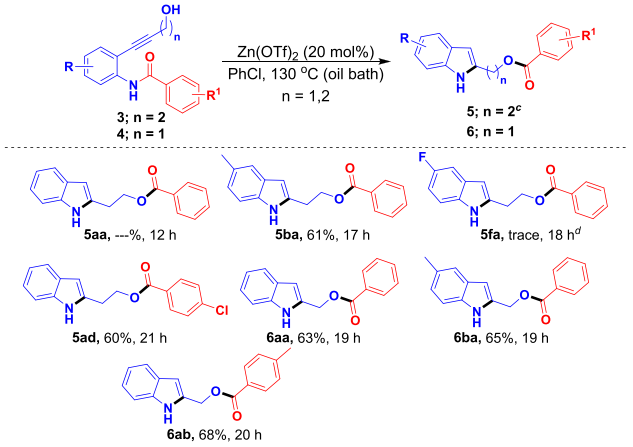
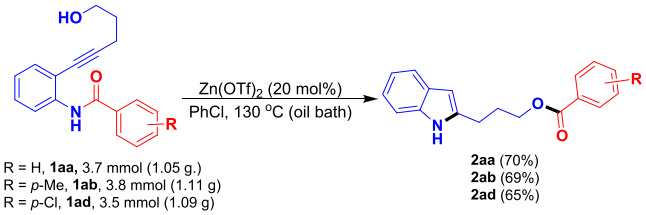
Scheme 3. Scope with 3-Butyn-1-ols and Propargyl Alcohols[a,b]



[a]All reactions were carried out using **3**/**4** (0.4 mmol) and $Zn(OTf)_2$ (20 mol %) in chlorobenzene (1.5 mL) at 130 °C (oil bath) in the sealed tube. [b]Isolated yields. [c]30 mol % of $Zn(OTf)_2$ was used. [d]An unknown compound was observed along with trace amount of desired product.

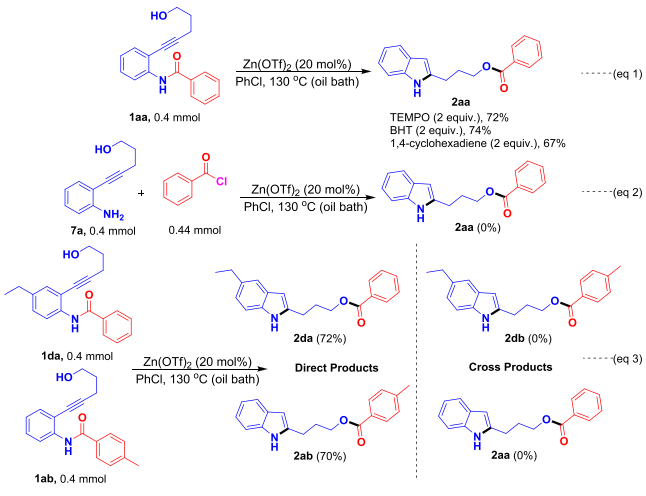
on TLC after reaction. However, compound **5fa** was observed in trace product along with an unknown compound. The practicality of this protocol was determined by carrying out the reactions on gram scale for three starting materials with different benzamide substitutions (Scheme 4).

Scheme 4. Gram Scale Reactions



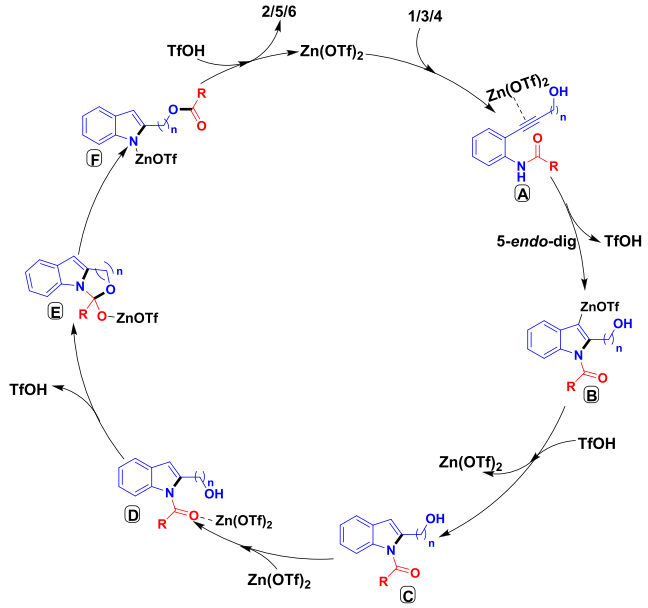
To understand the mechanism, we carried out a few control experiments as shown in Scheme 5. Radical inhibition studies of **1aa** under standard reaction conditions with TEMPO, BHT, and 1,4-cyclohexadiene gave **2aa** in 72%, 74%, and 71% yield, respectively (Scheme 5, eq 1). This result ruled out the radical pathway. Further, to understand the pathway of carbonyl group migration we carried out the reaction of 5-(2-aminophenyl)pent-4-yn-1-ol (**7a**) with benzoyl chloride under standard conditions (Scheme 5, eq 2). However, we did not observe the desired product **2aa**. This experiment confirms that the carbonyl group is migrating *insitu* during indole cyclization. In addition we also executed the crossover experiment (Scheme 5, eq 3). The equimolar quantities of **1da** and **1ab** were reacted under standard conditions and gave the direct products **2da** and **2ab**. The cross products **2db** and **2aa** were not detected by ^1H NMR. This experiment proves that the migration follows an intramolecular pathway.

Scheme 5. Control Experiments



Based on the control experiments carried out and previous reports,[9,16a] a plausible mechanism is outlined in Scheme 6. In the presence of catalytic amounts of Lewis acid, 2-alkynol benzamide derivatives (**1**/**3**/**4**) will undergo 5-*endo*-dig cyclization followed by protolysis to give a C2-substituted indole intermediate (**C**) and the Lewis acid will be regenerated. Later, the Lewis acid will again activate the amide group of the indole intermediate. This will be the driving force allowing alcohol to undergo nucleophilic substitution reaction and subsequent carbonyl migration to give the desired product (**2**/**5**/**6**).

Scheme 6. Plausible Mechanism



In summary, we have developed a Lewis acid catalyzed synthesis of C2-alkyl substituted indole derivatives from *o*-benzamido alkynols *via* migratory cycloisomerization. This protocol attains 100% atom economic efficiency with broad scope, varied functional group tolerance, and the carbon chain length of alkynol. Moreover, the crossover experiments also disclosed that the N,O-carbonyl group migration is happening *via* an intramolecular pathway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00971.

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General procedures; spectral characterizations; copies of ^{1}H, ^{13}C NMR spectra; HRMS data (PDF)

Accession Codes

CCDC 1986128 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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