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Indium-Catalyzed Amide Allylation of *N*-Carbonyl Imides: Formation of Azaspiro-γ-lactones via Ring Opening−Reclosure

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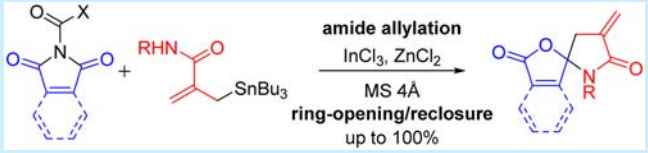
Supporting Information

ABSTRACT: A novel and facile synthesis of azaspiro-γ-lactones with a methylene−lactam framework from *N*-carbonyl imides is described. Mechanistic investigations provide evidence for a two-step reaction process involving $ZnCl_2$-promoted addition of β-amido allylindium species followed by an unexpectedly molecular-sieves-mediated ring opening−reclosure concomitantly with the loss of an *N*-carbonyl unit.



Nucleophilic allylation of aldehydes and ketones is undoubtedly an important carbon−carbon bond forming reaction, and a number of methods including enantioselective variants have been reported.[1] Among a variety of allylating reagents, allylsilanes,[2] allylstannanes,[3] and allylboronates[4] have found widespread use in syntheses of bioactive compounds because of their ready availability and ease of handling. In recent years, reactions using alternative metal reagents such as allylindium[5] and allylgallium species[6] have been developed. They are generally prepared in situ by oxidative insertion of low-valent metallic species into allyl halides or transmetalation with metal halides, allowing for chemoselective transformations of polyfunctionalized organic compounds.

In addition to conventional reactions using simple allylmetal reagents, allylation with functionalized ones has been of great importance due to broad utility in complex molecule synthesis.[7−9] In this context, we have reported the enantioselective synthesis of diversely substituted β-amido homoallyl alcohols **2** as a key precursor of bioactive α-methylene-γ-butyrolactones via indium-catalyzed allylation of aldehydes with β-amido allyltributylstannanes **1** (Scheme 1).[8] More recently, we have extended this reaction methodology to a wide range of isatin derivatives and acyclic α-ketoesters, where extremely high enantioselective synthesis of antineoplastic spirooxindole and its derivatives has been achieved.[9] Apparently, such amide allylation of carbonyl compounds offers a great advantage in the synthesis of potential drug candidates; however, no examples using imide derivatives have been reported in the literature to date.[10] Hence, it is a great challenge to extend our studies with imides **4** in order to provide new azaspiro-γ-lactone **II**, the azaspirobicyclic framework of which is found in natural products possessing significant bioactivities and thus has been attracting much attention from synthetic chemists as a challenging synthetic target.[11] Here we report a first example of catalytic amide allylation with *N*-carbonylimides to synthesize azaspiro-γ-lactone derivatives.

We initially investigated amide allylation of *N*-ethoxycarbonyl maleimide **4a** with *N*-phenyl-β-amido allylstannane **1a** in the presence of an excess amount of 4 Å molecular sieves (MS 4 Å) in CH_2Cl_2. When the reaction was conducted with 20 mol % of $Yb(OTf)_3$ or $Sc(OTf)_3$, no reaction occurred. In contrast, use of $In(OTf)_3$ provided a new product **5a** in 54% yield after 1 day of stirring at room temperature (Scheme 1c).[12] Alternatively, the reaction with $InCl_3$ (20 mol %) also gave the same product at an analogous level of product yield (55%). To our surprise, ^1H and ^{13}C NMR data for **5a** showed that the ethoxycarbonyl group originating from **4a** was completely lost, indicating that the expected compound **I** was not formed. High resolution mass spectral data for **5a** (m/z $[M]^+$ 241.0742) supported these observations, indicating molecular formula $C_{14}H_{11}NO_3$. Assignment with the help of DEPT experiments suggested that **5a** contains two lactam/lactone carbons (δ_c 167.5 and 169.4 ppm) and one quaternary hemiaminal carbon (δ_c 99.0 ppm). Furthermore, NOE experiments showed that a lactam ring is fused to an α,β-unsaturated-γ-lactone. Thus, the complete structure of **5a** was revealed to be 8-methylene-6-phenyl-1-oxa-6-azaspiro[4.4]non-3-ene-2,7-dione as shown in Scheme 1. Although **5a** was not our target molecule **I** or **II**, this

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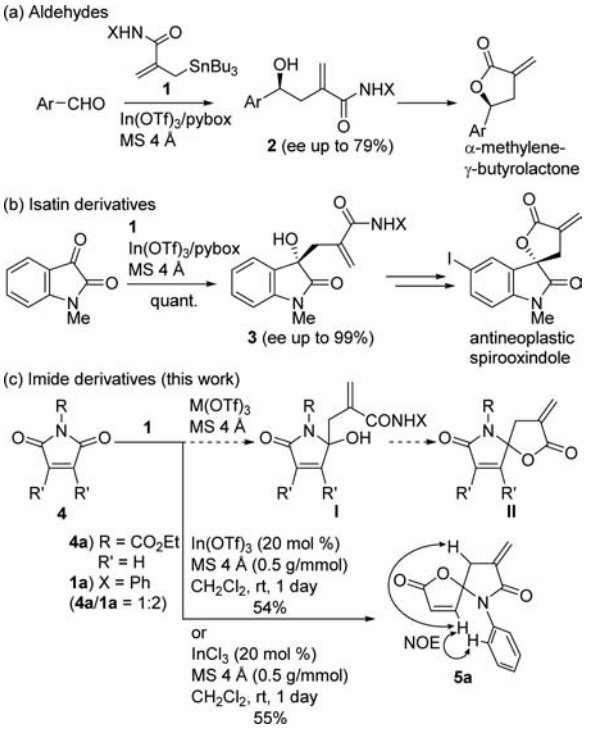
Scheme 1. Indium-Catalyzed Amide Allylation of Carbonyl Compounds with β-Amido Allylstannanes

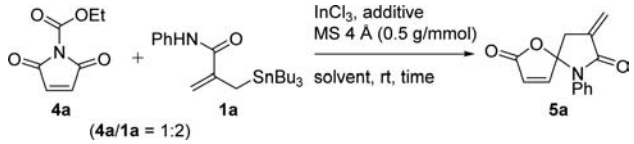


transformation can be regarded as an efficient approach allowing access to novel azaspiro-γ-lactones with a methylene–lactam framework. We therefore shifted our focus to establish the synthetic protocol which will provide new opportunities to develop these pharmaceutically attractive molecules.

Our next investigation of azaspiro-γ-lactone formation focused on the reaction of **4a** with **1a** in the presence of $InCl_3$ and various additives. In the absence of additives, **5a** was given in 80% yield even with a prolonged reaction time of 2 days (Table 1, entry 1). Use of $MgCl_2$, $CaCl_2$, $CuCl_2$, $FeCl_3$, or $SnCl_4$ along with $InCl_3$ proved to be ineffective under comparable conditions (Table 1, entries 2–6). While $ZnBr_2$ or ZnI_2 offered no improvement in the reaction rate (Table 1, entries 8 and 9), the reaction with $ZnCl_2$ (20 mol %) was completed within only 1 day to afford the desired product in 91% yield (Table 1, entry 7). The absence of $InCl_3$ or decreased catalyst loadings drastically deteriorated the reaction efficiency (Table 1, entries 10 and 11). Further solvent screening showed that dichloromethane gave the best result in comparison to toluene and acetonitrile (Table 1, entries 12 and 13). Thus, we could identify the optimal conditions which involve the use of 20 mol % of $InCl_3$ and $ZnCl_2$ and 0.5 g/mmol of MS 4 Å in CH_2Cl_2. The efficient reaction was reproduced under these conditions even when almost the same equivalent of **1a** was employed (Table 1, entry 14).

Table 2 shows the reaction of variously substituted imides **4** with amido allylstannanes **1**. By applying the optimum conditions used for entry 1, all the *N*-alkoxycarbonyl maleimides **4b–d** afforded the desired azaspiro-γ-lactone **5a** in good to excellent yields (71–91%), respectively (Table 2, entries 2–4). Surprisingly, substrates containing *N*-acetyl and *N*-phenylcarbamoyl groups **4e,f** could also be tolerable for this transformation, giving **5a** in diminished yields, respectively

Table 1. Metal and Solvent Effects for Azaspiro-γ-lactone Formation from 4a



entry	$InCl_3$ (mol %)	additive (mol %)	solvent	*t* (day)	yield (%)
1[a]	20	–	CH_2Cl_2	1	55
2	20	$MgCl_2$ (20)	CH_2Cl_2	4	72
3	20	$CaCl_2$ (20)	CH_2Cl_2	2	57
4	20	$FeCl_3$ (20)	CH_2Cl_2	2	68
5	20	$CuCl_2$ (20)	CH_2Cl_2	2	24
6	20	$SnCl_4$ (20)	CH_2Cl_2	2	29
7	20	$ZnCl_2$ (20)	CH_2Cl_2	1	91
8	20	$ZnBr_2$ (20)	CH_2Cl_2	2	71
9	20	ZnI_2 (20)	CH_2Cl_2	2	80
10	0	$ZnCl_2$ (20)	CH_2Cl_2	3	17
11	10	$ZnCl_2$ (10)	CH_2Cl_2	2	37
12	20	$ZnCl_2$ (20)	toluene	3	49
13	20	$ZnCl_2$ (20)	MeCN[b]	1	83
14[c]	20	$ZnCl_2$ (20)	CH_2Cl_2	1	91

[a]The reaction under the given conditions with a prolonged reaction time of 2 days afforded an 80% yield of **5a**. [b]Reaction was carried out with MS 3 Å. [c]Reaction was carried out with 1.2 equiv of **1a**.

(Table 2, entries 5 and 6). From these results, it should be emphasized that a wide range of carbonyl functions can serve as a leaving group. Next, we focused our attention on variation of substitution of the nitrogen group in **1**. When *N*-aryl (*p*-tolyl, *p*-anis, 4-*tert*-butylphenyl, 4-chlorophenyl, 2,6-xylyl, and 1-naphthyl) derivatives **1b–g** were treated with **4a** under the given conditions, **5b–g**[13] were produced in 89–100% yields, respectively (Table 2, entries 7–12). Alkyl substituents such as methyl and *n*-pentyl groups led to substantial loss of reactivity (55–67% yields) (Table 2, entries 13 and 14), whereas more sterically demanding *tert*-butyl group hampered this transformation, resulting in the isolation of amidoallyl adduct **6a** in 49% yield (Table 2, entry 15). These results strongly suggested that **5** would be produced from the amidoallyl intermediate **6** via ring opening–reclosure concomitantly with loss of an *N*-carbonyl unit.

We then examined the substrate scope of the azaspiro-γ-lactone formation. Reaction of *N*-ethoxycarbonyl succinimide, prepared from succinimide and ethyl chloroformate, with **1b** was examined, but a complex mixture of products was obtained presumably due to relatively poor electrophilicity of imide carbonyls. Meanwhile, investigations with substituted maleimides **4g** and **4h** showed that the efficiency of azaspiro-γ-lactone formation is strongly dependent on the substitution pattern of imide derivatives. Indeed, monosubstituted maleimide derivative **4g** gave a 93% yield of **5j** as a 2:1 mixture of regioisomers, although a longer reaction time was required (Table 2, entry 16). As for **4h**, the reaction failed to give any spirocyclic product and the corresponding amidoallyl adduct **6b** was predominantly generated in 82% yield (Table 2, entry 17). Further investigations for extending the reaction scope revealed that *N*-ethoxycarbonyl phthalimide **4i** reacted with **1a**, albeit sluggishly, leading to an 82% yield of **5k** whose structure was unambiguously confirmed by single crystal X-ray crystallographic analysis (Table 2, entry 18).[14] The reaction of **4i** with other stannyl reagents **1b,c,e,f** also successfully gave the

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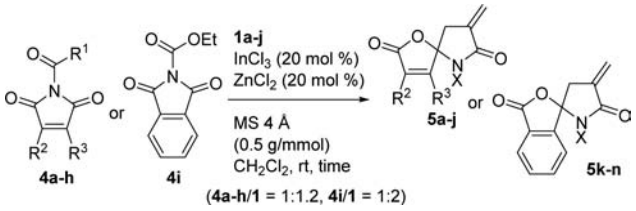
Table 2. Synthesis of Variously Substituted Azaspiro-γ-lactones 5



entry	4	R^1, R^2, R^3	1	X	*t* (day)	5 (yield %)
1	**4a**	OEt, H, H	**1a**	Ph	1	**5a** (91)
2	**4b**	O^{t}Bu, H, H	**1a**	Ph	1	**5a** (87)
3	**4c**	OMe, H, H	**1a**	Ph	1	**5a** (71)
4	**4d**	OBn, H, H	**1a**	Ph	1	**5a** (91)
5	**4e**	Me, H, H	**1a**	Ph	1	**5a** (59)
6	**4f**	NHPh, H, H	**1a**	Ph	4	**5a** (18)
7	**4a**	OEt, H, H	**1b**	*p*-tolyl	1	**5b** (100)
8	**4a**	OEt, H, H	**1c**	*p*-anis	2	**5c** (99)
9	**4a**	OEt, H, H	**1d**	4-^{t}Bu-Ph	3	**5d** (96)
10	**4a**	OEt, H, H	**1e**	4-Cl-Ph	1	**5e** (89)
11	**4a**	OEt, H, H	**1f**	2,6-xylyl	1	**5f** (99)
12	**4a**	OEt, H, H	**1g**	Nap[a]	1	**5g** (94)
13	**4a**	OEt, H, H	**1h**	Me	4	**5h** (55)
14	**4a**	OEt, H, H	**1i**	^{n}pentyl	4	**5i** (67)
15	**4a**	OEt, H, H	**1j**	^{t}Bu	3	–[b]
16	**4g**	OEt, Me, H	**1b**	*p*-tolyl	8	**5j** (93)[c]
17	**4h**	OEt, Me, Me	**1b**	*p*-tolyl	3	–[d]
18	**4i**	–	**1a**	Ph	3	**5k** (82)
19	**4i**	–	**1b**	*p*-tolyl	3	**5l** (55)
20	**4i**	–	**1c**	*p*-anis	3	**5m** (59)
21	**4i**	–	**1e**	4-Cl-Ph	3	**5n** (70)
22	**4i**	–	**1f**	2,6-xylyl	3	**5o** (76)

[a]Nap = 1-naphthyl. [b]Amidoallyl adduct **6a** (for structure, see Scheme 1, I; R = COOEt, R′ = H, X = ^{t}Bu) was obtained as a sole product in 49% yield. [c]**5j** and its regioisomer **5j′** (R^2 = H, R^3 = Me, X = *p*-tolyl) were obtained as an inseparable 2:1 mixture. [d]Amidoallyl adduct **6b** (for structure see Scheme 1, I; R = COOEt, R′ = Me, X = *p*-tolyl) was obtained in 82% yield.

corresponding products **5l–o** in 55% to 76% yields, respectively.

Finally, mechanistic investigations were undertaken to understand the role of additives. As in the case of transmetalation of allyltributylstannane with $InBr_3$,[5d] resonances of exomethylene protons of the sample, prepared by treatment of **1a** with $InCl_3$ (1 equiv) for 30 min in dichloromethane-d_2, were significantly shifted downfield relative to those of **1a** (H^a and H^b), suggesting formation of a new allylindium species (Figure 1a,b).[15] Subsequent nucleophilic attack of indium species thus prepared was dramatically promoted by using an equimolar amount of $ZnCl_2$, resulting in complete consumption of **4a** within 6 h (Figure 1c). We then examined this unexpected transformation with ring opening–reclosure of **6** into **5**. During the course of the substrate screening described in Table 2, we fortunately found that the intermediate **6c** was isolated in 47% yield at the reaction time of 1 day. When **6c** was treated only with 0.5 g/mmol of MS 4 Å, the reaction smoothly proceeded to afford **5k** in 84% yield. Use of MS 4 Å and $ZnCl_2$ still resulted in the predominant formation of the product. In contrast, reaction in the absence of molecular sieves gave **5k** in poor yields along with recovery of the starting material, despite employing $InCl_3$ and/or $ZnCl_2$ (Figure 1d). These results show

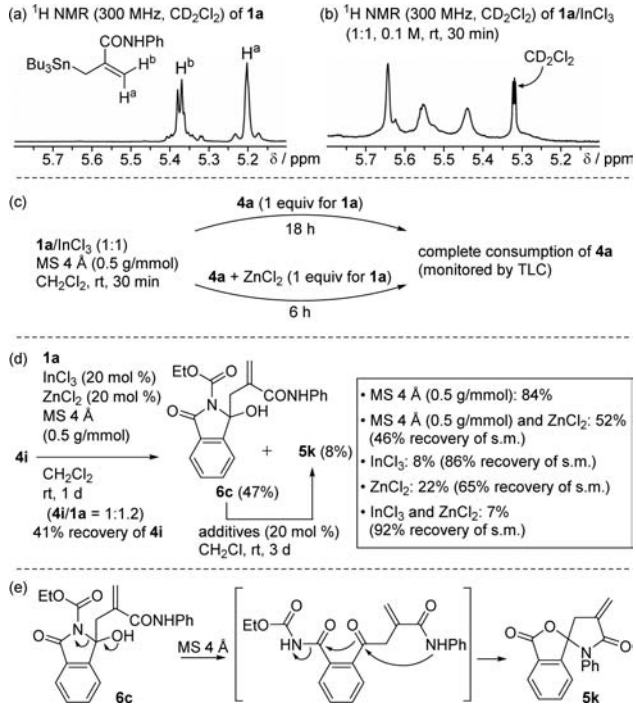


Figure 1. Mechanistic investigations of azaspiro-γ-lactone formation.

that the acidic and/or basic nature of molecular sieves[16] would be essential for efficient ring opening–reclosure, for which the mechanistic pathway is tentatively shown in Figure 1e. By combining all of these observations, we concluded that this unique transformation from imide derivatives **4** into azaspiro-γ-lactones with a methylene–lactam framework **5** involves two steps, that is, $ZnCl_2$-promoted amide allylation of **4** with allylindium species generated by transmetalation and subsequent molecular-sieves-mediated ring opening–reclosure concomitantly with loss of an *N*-carbonyl unit.

In conclusion, we have demonstrated the novel synthesis of azaspiro-γ-lactones with an *exo*-methylene–lactam ring via amide allylation of imide derivatives. This work represents a unique synthetic entry to provide the new class of azaspirocycle as well as an obvious expansion in the scope of the amide allylation and will open new opportunities for future development of potential drug candidates. Investigations including detailed mechanistic aspects and the enantioselective variant of this molecular-sieves-mediated ring opening–reclosure are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03021.

Experimental details and characterization data for all new compounds (PDF)

X-ray structure of **5k** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) *N*-Phenyl maleimide instead of an *N*-carbonyl unit gave no reaction upon treatment with **1a** in the presence of $In(OTf)_3$ or $InCl_3$.
(13) The NMR spectra of azaspiro-γ-lactone **5g** derived from **4a** and **1g** displayed two sets of signals (*ca.* 2:1), indicating the element of chirality attributed to axial chirality must be present in the structure. Their rotational barrier was so low that a diastereomerically pure sample gave an almost 1:1 mixture of atropisomers after heating at 40 °C in $CHCl_3$ for 3 h.
(14) Crystal data for **5k** (also see Figure S1 in the Supporting Information): monoclinic, space group $P2_1/n$, a = 9.2686(15) Å, b = 16.156(3) Å, c = 9.4109(16) Å, V = 1403.3(4) Å^3, Z = 4, ρ = 1.379 Mg m^{-3}, μ(Cu Kα) = 0.095 mm^{-1}, T = 173 K; in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0379 ($I > 2\rho(I)$), wR_2 = 0.0969, and GOF = 1.061 for 3171 reflections and 199 parameters (CCDC deposition number 1431150).
(15) The resonance assignable to allylic protons of the indium species (δ 2.63 ppm) was also shifted downfield relative to that of **1a** (δ 2.05 ppm) (Figure S2, Supporting Information).
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