Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 320

Received 16th November 2016,
Accepted 29th November 2016

DOI: 10.1039/c6ob02506d

www.rsc.org/obc

Indium-catalysed amide allylation of α-iminoamide: highly enantioselective synthesis of amide functionalised α-methylene-γ-butyrolactams†

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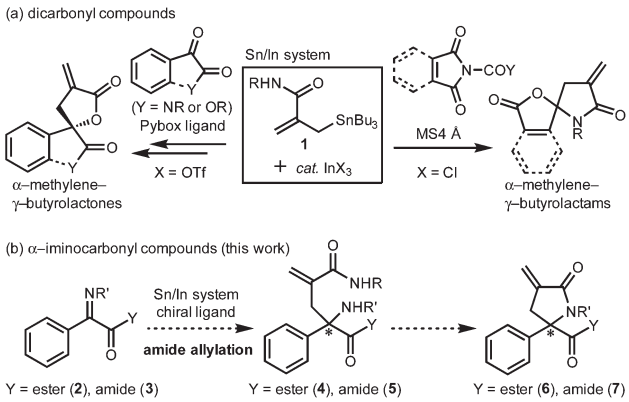
A highly enantioselective amide allylation of α-iminoamides has been achieved using catalytic amounts of $InCl_3$, $ZnCl_2$ and a BINOL derivative. This reaction allowed facile access to a variety of amide functionalised α-methylene-γ-butyrolactams in excellent yields with high enantioselectivities.

Allylation reactions of carbonyl compounds[1,2] and imines[1b–e,3] are important for the synthesis of potential drug candidates, because both homoallylic alcohol and homoallylic amine products are useful building blocks for the synthesis of bioactive heterocyclic compounds. In order to obtain the valuable products in an enantiomerically pure form, reactions using various combinations of allylating agents and chiral catalysts have been developed, and several examples have been successfully applied to the total synthesis of natural products.[2]

In the course of our studies on catalytic reactions using functionalised allylating agents,[4–6] we developed completely enantiocontrolled allylation of isatin derivatives[5a,b] or α-ketoesters[5c] with β-amido allylstannane **1** by employing In(pybox)$(OTf)_3$ as a catalyst. The products obtained in both reactions were readily cyclised under acidic conditions to furnish pharmaceutically potential α-methylene-γ-butyrolactones in optically pure forms (Scheme 1a). In addition, we recently reported that the reaction of **1** with imides provided a new class of azaspirocyclic compound containing an α-methylene-γ-butyrolactam skeleton.[6] Notably, α-methylene-γ-butyrolactams are considered as particularly attractive synthetic targets[7] because of their selective antitumour activity.[8] Nevertheless, synthetic methods for this type of compounds have not yet been fully established.[9] For these reasons, we decided to explore a new synthetic method for chiral ester/amide functionalised α-methylene-γ-butyrolactams **6**/**7** by applying indium-catalysed amide allylation to α-iminocarbonyl compounds **2**/**3**, respectively (Scheme 1b).



Scheme 1 Indium-catalysed allylation with β-amido allylstannanes.

Initially, we investigated the reaction of *N*-PMP-α-iminoester **2a** (R′ = PMP, Y = OMe) or amide **3a** (R′ = PMP, Y = NHPh) with **1a** (R = Ph) in the presence of In$(OTf)_3$, MS3 Å (ref. 10) and a chiral ligand (Scheme S1, ESI†). When the reactions of these substrates were carried out with (*S*,*S*)-Ph-Pybox, allylated products **4a** and **5a** were obtained in poor yields. In contrast, reactions with (*S*)-BINOL worked quite well to afford **4a** and **5a** in good yields with moderate enantioselectivities (74%, 34% ee and 86%, 32% ee, respectively). We then attempted the reaction in the presence of 3,3′- or 6,6′-diphenyl-BINOL[11a,b] to evaluate the effect of the substituent positions on BINOL. While utility of (*S*)-6,6′-diphenyl-BINOL yielded **4a** and **5a** with 32 and 38% ee, respectively, a much higher degree of asymmetric induction could be observed in the reaction of **3a** using (*S*)-3,3′-Ph_2-BINOL (58% ee).

These preliminary results with **3a** encouraged us to further optimise the reaction conditions (Table 1). Prior to extensive screening of BINOL derivatives, we examined the indium-catalysed reaction with metal additives.[6,12] Similarly to the good enantioselectivity observed as listed in entry 1 (89% ee),

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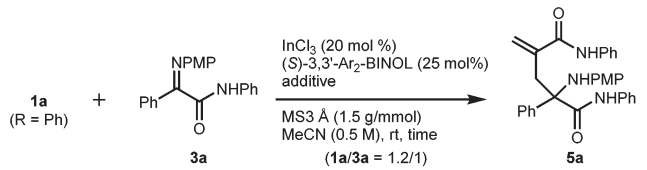
†Electronic supplementary information (ESI) available: X-ray structure of **8**. Experimental details, characterisation data, ^1H and ^{13}C NMR spectra for compounds **3**, **5** and **7**. CCDC 1517089. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob02506d

Table 1 Metal and ligand effects for the reaction of **3a** with **1a**[a]



Entry	Ar	Additive ([mol %])	t [h]	Yield [%] (ee [% ee])[b]
1	Ph	—	24	97 (89)
2	Ph	$NiCl_2$ (10)	24	91 (86)
3	Ph	$CoCl_2$ (10)	24	94 (84)
4	Ph	$ZnCl_2$ (10)	24	99 (95)
5[c]	Ph	$ZnCl_2$ (20)	24	99 (28)
6	2-Naphthyl	$ZnCl_2$ (10)	24	97 (95)
7	4-$NO_2C_6H_4$	$ZnCl_2$ (10)	15	93 (90)
8	4-MeC_6H_4	$ZnCl_2$ (10)	2	97 (94)
9	4-MeC_6H_4	$ZnCl_2$ (10)	4	99 (96)
10[d]	4-MeC_6H_4	$ZnCl_2$ (10)	9	92 (95)
11[e]	4-$MeOC_6H_4$	$ZnCl_2$ (10)	5	92 (96)
12[d]	2,6-$Me_2C_6H_3$	$ZnCl_2$ (10)	24	98 (63)
13[d,f]	4-MeC_6H_4	$ZnCl_2$ (5)	24	88 (75)

[a] All reactions were carried out with **1a** in dry MeCN in the presence of $InCl_3$ (20 mol%), (*S*)-3,3′-Ar_2-BINOL (25 mol%), additive and MS3 Å (1.5 g $mmol^{-1}$) ar r.t. under an Ar atmosphere. [b] The ee values were determined by HPLC analysis using Daicel Chiralpak IC. [c] Reaction performed in the absence of $InCl_3$. [d] Reaction performed at 0 °C. [e] Reaction performed at −10 °C. [f] Reaction performed in the presence of 10 mol% of $InCl_3$ and 13 mol% of ligand.

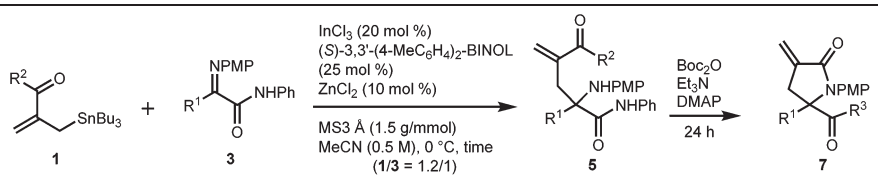
the reaction using $NiCl_2$ or $CoCl_2$ gave comparable results (Table 1, entries 2 and 3). The beneficial effect on this allylation could be obtained in the reaction employing $ZnCl_2$ (Table 1, entry 4, 95% ee), while **5a** was produced with 28% ee when the reaction was carried out without $InCl_3$ (Table 1, entry 5). From these results, the use of $InCl_3$ and $ZnCl_2$ was found to be suitable for this reaction.

Next, we focused our attention on the effect of 3,3′-substituents of BINOL. The use of BINOL derivatives bearing 2-naphthyl[11a] or 4-substituted phenyl groups[11d,e] led to excellent enantioselectivities (Table 1, entries 6–11, 90–96% ee), however, introduction of a more sterically demanding 2,6-dimethylphenyl group[11c] or reduced catalyst loading resulted in a decrease of enantiomeric excess (Table 1, entries 12 and 13). Thus, the reaction conditions shown in entry 10 proved to be optimum[13] and were used for further investigation.

To explore the scope regarding the substituent R^1, imine **3a** was subjected to the reaction with various *N*-substituted β-amido allylstannanes (Table 2). *N*-Arylamido and *N*-alkylamido derivatives **1b–g** afforded the corresponding adducts **5b–g** in quite high yields with good to excellent enantioselectivities, respectively (Table 2, entries 2–7).[14] We further investigated the substrate effect with respect to α-iminoamides. Reactions of **3b,c** that bear electron-donating (4-methoxyphenyl) or electron-withdrawing (4-trifluoromethylphenyl) groups gave results comparable to that with the phenyl derivative **3a** (Table 2, entries 8 and 9). Due to lower reactivity of the naphthyl derivative **3d** relative to the phenyl derivatives, increase of both catalyst loading and reaction period was required to obtain **5j**, resulting in a moderate ee value (Table 2, entry 10).

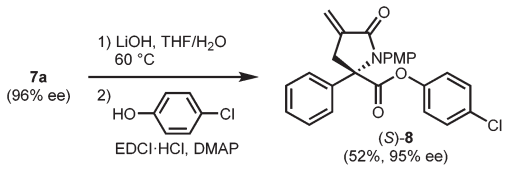
With a variety of homoallylic amine products in hand, subsequent attempt to convert them into α-methylene-γ-butyrolactams **7** was made. Treatment of **5a** with Boc_2O under basic conditions smoothly provided the corresponding α-methylene-γ-butyrolactam **7a** in 98% yield (Table 2, entry 1). It is remarkable that the enantiomeric excess remained con-

Table 2 Scope of amide allylation and lactamisation



Entry	**1** (R^2)	**3** (R^1)	t [h]	**5**	Yield of **5** [%] [ee (/%)][a]	**7** (R^3)	Yield of **7** [%] [ee (/%)][a]	Abs config.[b]
1	**1a** (NHPh)	**3a** (Ph)	4	**5a**	99 (96)	**7a** (N(Boc)Ph)	98 (96)	*S*
2	**1b** (NH(4-MeC_6H_4))	**3a**	6	**5b**	99 (91)	**7a**	98 (91)	*S*
3	**1c** (NH(4-$MeOC_6H_4$))	**3a**	6	**5c**	98 (92)	**7a**	96 (92)	*S*
4	**1d** (NH(4-^{t}BuC_6H_4))	**3a**	6	**5d**	98 (92)	**7a**	97 (92)	*S*
5	**1e** (NH(Nap))[c]	**3a**	6	**5e**	99 (94)	**7a**	98 (93)	*S*
6	**1f** (NH(4-ClC_6H_4))	**3a**	18	**5f**	96 (90)	**7a**	90 (90)	*S*
7	**1g** (NH(^{n}C_5H_{11}))	**3a**	19	**5g**	92 (82)	**7a**	95 (80)	*S*
8	**1a**	**3b** (4-$MeOC_6H_4$)	3	**5h**	96 (93)	**7b** (N(Boc)Ph)	90 (92)	(*S*)[d]
9	**1a**	**3c** (4-$CF_3C_6H_4$)	5	**5i**	99 (95)	**7c** (N(Boc)Ph)	97 (95)	(*S*)[d]
10[e,f]	**1a**	**3d** (Nap)[c]	66	**5j**	94 (57)	**7d** (N(Boc)Ph)	90 (57)	(*S*)[d]

[a] The ee values were determined by HPLC analysis using Daicel Chiralpaks IB (for **5i**), IC (for **5a**, **5f–h** and **5j**), IE (for **5b–e**, **7c** and **7d**) and IF (for **7a** and **7b**). [b] Absolute configuration of both lactams **7** and their precursors **5**. [c] Nap: 1-naphthyl. [d] The configuration was tentatively assigned on the basis of reaction mechanisms. [e] Reaction performed at room temperature. [f] 40 mol% of $InCl_3$, 50 mol% of 3,3′-(4-MeC_6H_4)$_2$-(*S*)-BINOL and 20 mol% of of $ZnCl_2$ were used.



Scheme 2 Transformation of **7a** into **8**.

stant in the course of this transformation. Other substrates bearing various substituted amido groups **5b–g** as well as aryl groups **5h–j** were also successfully cyclised under the identical conditions, affording the corresponding lactams **7a–d** in excellent yields with complete retention of enantiomeric purities (Table 2, entries 2–10).

We next turned to determine the absolute configuration of the newly formed stereocenter through single-crystal X-ray diffraction analysis using the anomalous dispersion method.[15] α-Methylene-γ-butyrolactam **7a** (96% ee) prepared from **5a** could be converted into the crystalline 4-chlorophenyl ester **8** through basic hydrolysis followed by esterification (Scheme 2). The enantiomeric purity of the sample was found to be maintained during the reactions. The ester **8** was further purified by recrystallisation from chloroform/hexane to afford X-ray quality crystals. Single-crystal X-ray diffraction analysis showed that the molecules adopt the chiral triclinic space group *P*1 with the Flack parameter as low as 0.1 (0), clearly demonstrating that the absolute configuration of the newly formed stereocentre is *S* (Fig. S1, ESI†).[15,16] Furthermore, the configurations of the major enantiomers of all the lactams **7a** in Table 2 were also unambiguously confirmed to be *S* by comparing their chiral HPLC retention time with that of (*S*)-**7a**.[17]

To understand the role of $InCl_3$ and $ZnCl_2$, several NMR experiments were performed. As can be seen in Table 1 (entries 1–5), the use of $InCl_3$ and BINOL is necessary for the asymmetric induction. It can be assumed that $InCl_3$ would contribute to the asymmetric induction through complexation with BINOL.[18] The ^{1}H NMR spectrum of an equimolar mixture of **3a**, $InCl_3$ and a BINOL derivative showed that all the resonances attributed to **3a** were significantly shifted downfield relative to those of original **3a** (Fig. S2, ESI†). This observation suggests that the substrate would coordinate to the In–BINOL complex.

Meanwhile, upon treatment of an allylindium species, prepared by mixing **1a** and $InCl_3$,[6] with $ZnCl_2$, a new species was formed that we tentatively assigned as an allylzinc species, as shown by ^{1}H NMR analysis (Fig. S3, ESI†). In a control experiment, no reaction occurred when **1a** was directly treated with $ZnCl_2$. These results indicate that $InCl_3$ would promote *in situ* generation of the allylzinc species from allylstannanes **1** *via* formation of the allylindium intermediate. Consequently, we postulated at present that the reaction of α-iminoamides with **1** takes place through nucleophilic addition of allylindium and allylzinc species to imines activated by the In–BINOL complex.

In conclusion, we have demonstrated the new catalytic enantioselective allylation of α-iminoamides. The reaction of α-iminoamides with β-amido allylstannanes in the presence of $InCl_3$, $ZnCl_2$ and a BINOL derivative was found to be quite effective to give high enantioselectivity. This work represents not only a significant expansion of the scope of amide allylation but also an achievement in the facile synthesis of pharmaceutically potential α-methylene-γ-butyrolactams. The successful development of the reaction showing the wide substrate generality and the high level of stereocontrol will provide new opportunities for the future development of promising drug candidates bearing methylenelactam structures. Further investigations on the synthetic application of this methodology are currently underway in our laboratory.

Acknowledgements

We thank Mr Ikuhei Ikeda (Shizuoka University) for partial support of this research. This work was supported financially in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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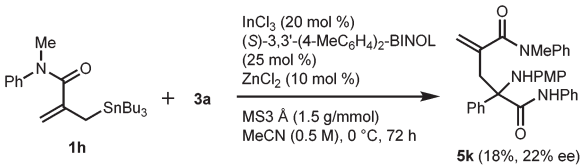
13 Reactions in other solvents such as toluene and CH_2Cl_2 gave **5a** with 66% and 68% ee, respectively.

14 In contrast, the reaction with tertiary amide for 1 h resulted in poor yield and enantioselectivity. We additionally examined the reaction of **3a** with β-ester functionalised allylstannane (R^1 = OMe), failing to give the desired allylated product. These results suggest that the N–H functionality of the secondary amide group present in allylstannanes would play an important role in enhancing reactivity and enantioselectivity.



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16 Crystal data for **8**: triclinic, space group *P*1, a = 6.5505(3) Å, b = 8.7111(4) Å, c = 9.9103(5) Å, V = 527.35(4) Å^3, Z = 1, ρ = 1.366 Mg m^{-3}, $\mu(CuK_\alpha)$ = 1.875 mm^{-1}, T = 173 K; in the final least-squares refinement cycles on F^2, the model converge at R^1 = 0.0297 ($I > 2\sigma(I)$), wR^2 = 0.0766, and GOF = 1.031 for 2571 reflections and 281 parameters (CCDC deposition number 1517089).

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