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Catalytic amide allylation of α-ketoesters: extremely high enantioselective synthesis of ester functionalised α-methylene-γ-butyrolactones†

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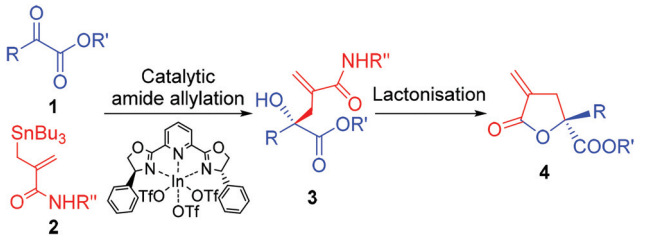
This communication reports a significant breakthrough on the novel catalytic amide allylation to the acyclic α-ketoester systems, achieving satisfactorily high yields and extremely high levels of the asymmetric induction to allow for highly enantioselective synthesis of ester functionalised α-methylene-γ-butyrolactones.

Carbonyl allylation with β-amido-functionalised allylstannanes,[1] which we call an "amide allylation",[2] has emerged as a powerful method that can facilitate high-yielding synthesis of amido-appended homoallylic alcohols with very high levels of enantiocontrol under the influence of chiral indium catalysts.[3–5] The synthetic appeal of this method lies in ready accessibility to enantiomerically enriched or pure forms of pharmaceutically meaningful α-methylene-γ-butyrolactones[6] *via* acid-promoted lactonisation of the allylated products. Our research group has recently developed a fully mechanistic understanding of the origin of the enantioselectivity for the amide allylation of isatin substrates, and also succeeded in demonstrating the broad utility of this approach to deliver a variety of optically active spiro-fused 2-oxindole/α-methylene-γ-butyrolactones.[4,5] As part of our continuing program to develop this catalytic system, we directed our efforts to extend our investigations toward applying the methodology to acyclic substrates, instead of the heterocyclic isatins. To address this challenge, a rational design of practical reaction systems can be derived from the lessons acquired from the earlier work that ketoamide structural motifs of isatins play a key role in enhancing the catalytic performance.[5] In light of this knowledge, it is suggested that α-ketoesters sharing the common 1,2-dicarbonyl backbone structures may serve as prospective candidates for enantioselective catalysis of the amide allylations. Nevertheless, many previous reports have underscored the inherent difficulty of obtaining notable success in the catalytic asymmetric addition to the α-ketoester systems. The most successful systems for this type of reaction have limited the reagents to have only structurally simple substituents, as exemplified by unfunctionalised alkylating agents, yet a promising way to achieve exceedingly high levels of enantioselectivity remains firmly out of reach. Thus, the realization of the strategy for enantioselective catalytic transformation of α-ketoesters capable of overcoming these drawbacks continues to be a highly challenging endeavour for synthetic organic chemists.[7] In this communication, we disclose a significant breakthrough on the catalytic amide allylation on the acyclic α-ketoester systems represented by structure **1** (Scheme 1), achieving satisfactorily high yields and extremely high levels of the asymmetric induction to allow for enantioselective synthesis of ester functionalised α-methylene-γ-butyrolactones.

The previous results on the amide allylation of isatins have highlighted the potential use of *N*-(*p*-tolyl)-β-amido allyltributylstannane **2a** and a chiral catalyst, prepared from $In(OTf)_3$ and (*S*,*S*)-phenyl-pybox ligand,[8] in exerting the highest level of enantiocontrol.[4,5] Thus, the initial attempt was made to apply these reaction conditions to methyl benzoylformate **1a**. When this substrate (*c* 0.5 mol L^{-1}) was subjected to react with **2a** (1.2 equiv.) in anhydrous MeCN in the presence of the catalyst (10 mol%) and MS3 Å (0.5 g $mmol^{-1}$) at r.t., the amide allyla-



Scheme 1 Synthetic route for α-methylene-γ-butyrolactones.

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Table 1 Scope of amide allylation[a] and lactonisation[b]

Entry	R, R′ (**1**)[c]	R″ (**2**)[c]	t^d [h]	**3**[c]	Yield of **3**[e] [%] (ee[f] [%])	t^g [h]	**4**[c]	Abs config.[h]	Yield of **4**[e] [%] (ee[f] [%])
1	Ph, Me (**1a**)	*p*-tolyl (**2a**)	18	**3a**	99 (99)	9	**4a**	*S*	84 (98)
2	Ph, Me (**1a**)	Ph (**2b**)	24	**3b**	99 (98)	12	**4a**	*S*	85 (97)
3	Ph, Me (**1a**)	*p*-anis (**2c**)	15	**3c**	99 (99)	11	**4a**	*S*	98 (99)
4	Ph, Me (**1a**)	*p*-*t*BuPh (**2d**)	16	**3d**	98 (98)	8	**4a**	*S*	97 (96)
5	Ph, Me (**1a**)	1-naph (**2e**)	24	**3e**	99 (93)	10	**4a**	*S*	82 (93)
6	Ph, Me (**1a**)	nC_5H_{11} (**2f**)	15	**3f**	98 (96)	26	**4a**	*S*	77 (96)
7	Ph, Me (**1a**)	*t*Bu (**2g**)	18	**3g**	98 (96)	49	**4a**	*S*	68 (94)
8	Ph, Me (**1a**)	*p*-ClPh (**2h**)	24	**3h**	98 (97)	11	**4a**	*S*	97 (95)
9	Ph, Bn (**1b**)	*p*-anis (**2c**)	13	**3i**	97 (98)	11	**4b**	*S*	99 (98)
10	Ph, *i*Pr (**1c**)	*p*-anis (**2c**)	13	**3j**	96 (97)	11	**4c**	*S*	97 (97)
11	Me, Me (**1d**)	*p*-anis (**2c**)	66[i]	**3k**	72 (99)	11	**4d**	*R*	86 (99)

[a] The amide allylations of **1** were carried out with **2** (1.2 equiv.) in anhydrous MeCN in the presence of the chiral catalyst (10 mol%) and MS3 Å (0.5 g $mmol^{-1}$) at r.t. under an argon atmosphere. [b] The lactonisations of **3** were carried out with PTSA (1.1 equiv.) in DCE at 50 °C (60 and 80 °C for **3f** and **3g**, respectively). [c] Structures of **1–4**, which indicate R, R′ and R″ substituents, can be found in Scheme 1. [d] Reaction times required for amide allylation under the standard conditions until complete consumption of starting materials (incomplete consumption of the starting material was observed in the case of entry 11). [e] Isolated product yields. [f] The ee values were determined by HPLC analysis with Daicel Chiralpaks IA (for **3d**), IC (for **3e**, **3f**, **3i** and **3j**), IE (for **4a–d**) and IF (for **3a–c**, **3g**, **3h** and **3k**). [g] Reaction times required for lactonisation under the standard conditions until complete consumption of starting materials. [h] Absolute configurations of both the lactones **4** and their homoallylic precursors **3**. [i] High catalyst loading (20 mol%) was employed.

tion proceeded quantitatively to afford the allylated product **3a** over a time period of 18 h. To our delight, HPLC analysis on a chiral stationary phase column (Daicel Chiralpak IF) showed that this product was obtained with an excellent ee value of 99% (Table 1, entry 1). The results obtained here suggest that a mechanistic scenario similar to the previously proposed one may apply to the series of α-ketoester systems.[5] We next investigated the reaction scope of **1a** with regard to variation of the substituents on the stannylated reagents. Indeed, a number of reagents containing diverse amide groups **2b–h** reacted in the same way, regardless of whether the aromatic or alkyl groups were incorporated, to lead similarly to excellent yields (98–99%) and enantioselectivities (93–99% ee) of the corresponding homoallylic alcohols **3b–h**, respectively, thus showing the potential generality of the reaction (Table 1, entries 2–8). From these results, we found that the *N*-(*p*-anis) analogue **2c** gave the highest yield and enantioselectivity (99%, 99% ee) for a slightly shorter reaction period (15 h) and would be a more preferable reagent than **2a** (Table 1, entry 3). Encouraged by the preceding results, we then investigated further applicability of the catalytic amide allylation to the other α-ketoesters to encompass a broader substrate scope. To this end, three additional entries of the substrates **1b–d** were tested as α-ketoester alternatives. Upon subjection of **1b** and **1c** to the amide allylation conditions involving the use of **2c**, clean and smooth reactions again took place to afford the expected products **3i** and **3j** in very high yields (97 and 96%) with excellent levels of enantioselectivity (98 and 97% ee), respectively (Table 1, entries 9 and 10). On the other hand, methyl pyruvate **1d** reacted sluggishly under the standard conditions,[9] but performing the same reaction with a catalyst loading of 20 mol% yielded the product **3k** in a considerably improved yield with the maximum ee value of 99%. Considering the fact that this substrate, the smallest member of the series, shows the excellent asymmetric induction, it is intuitive to expect that this

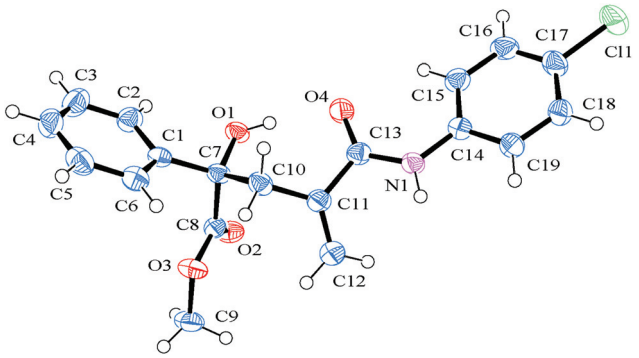
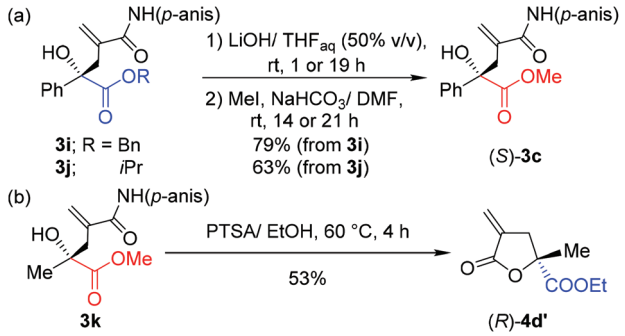


Fig. 1 ORTEP diagram for the absolute configuration of (*S*)-**3h** with 50% thermal ellipsoid probability.

methodology will have far more general applicability of the α-ketoesters, tolerating a variety of structural modifications without a loss of high catalytic performance.

Next, our focus turned to stereochemical assignment for predominant isomers of the obtained products. In order to probe this issue, single crystal X-ray diffraction analysis was undertaken on the chloro-functionalised homoallylic alcohol **3h**, which was expected to have larger anomalous dispersion effects due to the presence of the heavy atom element.[10] This analytical technique allowed unequivocal determination of its absolute stereochemistry on the basis of the satisfactory Flack parameter value, revealing *S* configuration at the newly formed stereogenic centre (Fig. 1).[11] With this information in hand, the absolute configurations of **3a–h** could be established by converting them into structurally uniform α-methylene-γ-butyrolactones and by correlating their chiral HPLC profiles with that for the authentic standard prepared by the same method from (*S*)-**3h**. For this conversion, an approach with *p*-toluenesulfonic acid (PTSA) proved effective on heating in 1,2-dichloro-



Scheme 2 Transformations for absolute configuration determinations.

ethane (DCE) at 50 °C,[4,5] and could be used to furnish the common lactones, denoted as **4a**, without noticeable degradation of the stereochemical qualities for all cases (Table 1, entries 1–8). The comparative analysis of the HPLC results showed remarkable consistency of the stereochemical preferences, providing clear evidence that all the homoallylic precursors analysed here include the *S* absolute configurations resulting mechanistically from *Re*-face additions of **2** onto the prochiral carbonyl centres of **1**.[5]

In a similar manner, **3i–k** were shown to undergo the PTSA-promoted lactonisation to afford **4b–d** in satisfactorily high isolated yields, while still maintaining the excellent enantiopurities (Table 1, entries 9–11). Based on the above results, stereochemical assignments of **3i** and **3j** were also achieved by replacing their ester functionalities with the methyl one for comparison with the authentic standard of (*S*)-**3c** (Scheme 2a). After the transformation through hydrolysis with LiOH and subsequent esterification with MeI to obtain the corresponding methyl esters **3c**, the absolute configurations of these compounds, together with those of the respective lactones, were established by the chiral HPLC analyses to be of the same *S*-chirality, giving a clear indication of the same preferences for the *Re*-face attacks involved in the amide allylations of **1b** and **1c**. On the other hand, the absolute stereochemistry of **3k**, which remained unclear, could be assigned on the basis of comparison with the reported optical rotation.[12] In this case, this material was needed to be transformed to **4d′**, an ethyl ester analogue of **4d**, *via* simultaneous ester exchange/lactonisation upon treatment with ethanolic PTSA at 60 °C, thereby obtaining the desired product (Scheme 2b). By comparison of its optical rotation with the literature data, the absolute stereochemistry of **4d′** was assigned to be *R*, reflecting the fact that **3k** and **4d** share the same configurations, again indicative of the involvement of the same stereochemistry determining step. Finally, it is indeed important to note that the overall assessment of the stereochemical outcomes shows complete uniformity of the *Re*-face selectivity, which is in accordance with our mechanistic picture of how the previous catalytic system functioned,[5] leading to a clear perspective on the origins of the excellent levels of asymmetric induction observed for the current catalytic system.[13]

In conclusion, we have developed the first catalytic enantioselective amide allylation of acyclic α-ketoesters, which achieved excellent reaction performance while exemplifying the wide substrate and reagent generality to provide ready access to a variety of the ester functionalised enantiopure α-methylene-γ-butyrolactones. Future studies will explore the full synthetic potential of these reaction systems and drive expansion of the amide allylation method to be of more general utility.

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11 Crystal data for **3h** (recrystallized from chloroform–hexane solution): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.6270(3) Å, b = 7.9739(3) Å, c = 32.9949(14) Å, $\alpha = \beta = \gamma$ = 90°, V = 1743.55(13) Å^3, Z = 4, ρ = 1.371 Mg m^{-3}, $\mu(\mathrm{Cu_{K\alpha}})$ = 2.145 cm^{-1}, T = 173 K; in the final least-squares refinement cycles on F^2, the model converged at R_1 = 0.0400 ($I > 2\sigma(I)$), wR_2 = 0.1097, GOF = 1.026 and Flack absolute structure parameter = 0.055(6) for 3176 reflections and 228 parameters (CCDC deposition number 1003520).

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13 Further experiments showed that methyl acetoacetate and methyl levulinate, representing β- and γ-ketoesters, respectively, failed to undergo the amide allylation under the standard reaction conditions, resulting in complete recovery of the starting materials. This fact strongly suggests that the α-dicarbonyl functionalities of the substrates meet the necessary structural requirements for the effective catalysis of the enantioselective amide allylation.