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Effective 1,5-stereocontrol in Pd(0)/InI promoted reactions of chiral *N*-Ts-4-vinylazetidin-2-ones with aldehydes. An efficient entry into nonracemic semi-protected (3*Z*)-2,6-*anti*-enediols†

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ε-Amido-allylindiums generated *in situ* from *N*-Ts-4-vinylazetidin-2-ones in the presence of 2 eq. of InI and catalytic amounts of $Pd(PPh_3)_4$ react with a number of aromatic and aliphatic aldehydes with effective remote 1,5-stereocontrol to afford (3*Z*)-2,6-*anti*-enediols as major products in good yields and with excellent diastereoselectivity.

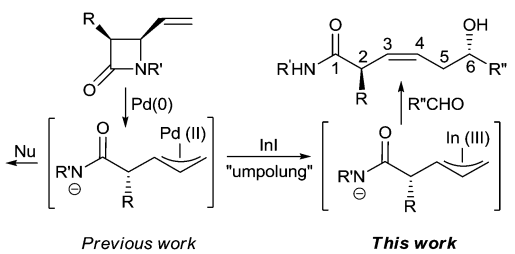
The synthesis of homoallylic alcohols *via* the reaction of allylmetal reagents with carbonyl compounds is one of the most effective C–C bond formation methods in organic synthesis.[1] Among many reagents the nontoxic, water tolerant allylindiums generated *in situ* by reductive transmetalation of π-allylpalladium(II) complexes, providing high yields and often excellent selectivity under mild reaction conditions, constitute very interesting alternatives.[2] Since the pioneering work by Marshal on the reactions of chiral nonracemic allenylindiums generated from enantioenriched secondary propargylic mesylates in the presence of InI and 5 mol% Pd(0) catalyst and their additions to aldehydes,[2d] several interesting articles using this methodology have appeared during the last decade.[2e–o] However, the utility of 4-vinylazetidin-2-ones as precursors of chiral ε-amido-allylindiums and regio- and stereoselectivity of their additions to electrophiles have not been reported so far.

Due to well-known antibiotic activity of β-lactams (azetidin-2-ones) a great number of methods of asymmetric syntheses of these types of compounds have been developed. Thus a variety of them are readily available in both enantiomeric forms in excellent optical purity.[3] The high reactivity of β-lactams, resulting from the strained 4-membered ring, the high chirality content that can be easily transferred to a variety of products and the rigidity of their structure often make the reactions involving them very stereoselective, which has engendered many synthesis methods of a number of derivatives not containing a β-lactam fragment using these compounds as chiral building blocks.[4] Although the transformation of 4-vinyl-azetidin-2-ones by C–N bond cleavage using Pd(0) catalysts and subsequent reactions of electrophilic Pd(II) complexes generated in this manner with nucleophiles have been seldom reported,[5] umpolung of these species by transmetalation and subsequent reactions with electrophiles including carbonyl compounds have not been described yet.

In this communication, we wish to report the highly stereoselective synthesis of (3*Z*)-2,6-*anti*-enediols by umpolung of β-lactams and their addition to aldehydes in the presence of InI and a catalytic amount of $Pd(PPh_3)_4$ for the first time (Scheme 1). The 2,6-*anti*-enediols obtained in this manner can be easily transformed into a variety of linear and heterocyclic derivatives, which is exemplified in the following article.

As a model compound, racemic *N*-Ts-4-vinylazetidin-2-one (±)-**2**, readily available in two steps from known β-lactam (±)-**1**, was chosen.[6] A bulky OTIPS substituent on C-3 of the β-lactam ring was expected to provide good stereoselectivity of the addition step, while a strongly electron withdrawing Ts group attached to the nitrogen atom, facilitating Pd(0)-promoted C–N bond cleavage.

Initially, the formation of the corresponding allylindium from (±)-**2** and its subsequent addition to benzaldehyde under the conditions developed in Takemoto's group was attempted.[2e,f] As shown in Table 1 (entry 1), the reaction gave exclusively 2,6-*anti*-enediols (±)-**3a** and (±)-**3b**, in 88% total yield, with moderate (*Z*)-selectivity and significant remote 1,5-asymmetric induction.



Scheme 1 Reactions of π-allylpalladium(II) complexes generated from β-lactams.

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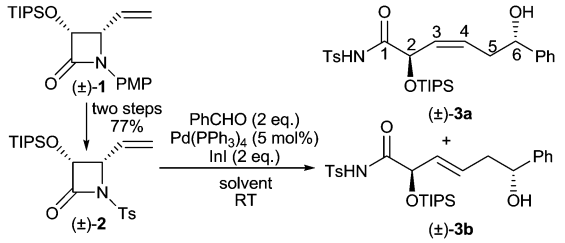
† Electronic Supplementary Information (ESI) available: Experimental details, full characterization data and copies of NMR spectra for all new compounds. CCDC 1048357. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc01485a

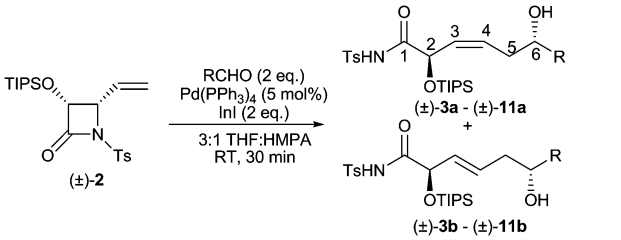
Table 1 Solvent effect on the $Pd(PPh_3)_4$/InI-mediated addition of *N*-Ts-4-vinylazetidin-2-one (±)-**2** to benzaldehyde



Entry	Solvent	Time	(±)-**3a** yield[a] [%]; (d.r.)[b]	(±)-**3b** yield[a] [%]; (d.r.)[b]
1	THF	30 min	59 (91 : 9)	29 (69 : 31)
2	Dioxane	3 h	57 (86 : 14)	28 (71 : 29)
3	DME	1 h	68 (87 : 13)	14 (63 : 37)
4	DMF	12 h	22 (89 : 11)	67 (80 : 20)
5	NMP	12 h	26 (86 : 14)	69 (78 : 22)
6	MeOH	3 days	Complex mixture	
7	THF/HMPA (4 : 1)	30 min	71 (95 : 5)	14 (91 : 9)
8	THF/HMPA (3 : 1)	30 min	80 (95 : 5)	15 (92 : 8)
9	THF/HMPA (2 : 1)	30 min	81 (96 : 4)	16 (92 : 8)
10	THF/DMPU (3 : 1)	30 min	29 (90 : 10)	68 (77 : 23)

[a] Isolated yields. [b] Assayed by ^{1}H NMR integration.

Table 2 $Pd(PPh_3)_4$/InI-mediated addition of *N*-Ts-4-vinylazetidin-2-one (±)-**2** to aromatic and aliphatic aldehydes



Entry	R	(3*Z*)-2,6-Enediol; yield[a] [%] (d.r.)[b]	(3*E*)-2,6-Enediol; yield[a] [%] (d.r.)[b]
1	Ph	(±)-**3a** 80 (95 : 5)	(±)-**3b** 15 (92 : 8)
2	*p*-CN-Ph	(±)-**4a** 81 (95 : 5)	(±)-**4b** 17 (94 : 6)
3	*p*-OMe-Ph	(±)-**5a** 74 (93 : 7)	(±)-**5b** 17 (88 : 12)
4	Et	(±)-**6a** 65 (92 : 8)	(±)-**6b** 33 (79 : 21)
5	i-Pr	(±)-**7a** 70 (94 : 6)	(±)-**7b** 27 (85 : 15)
6	*t*-Bu	(±)-**8a** 79[c] (97 : 3)	(±)-**8b** 17[c] (92 : 8)
7		(±)-**9a** 65 (94 : 6)	(±)-**9b** 20 (82 : 18)
8		(±)-**10a** 70 (95 : 5)	(±)-**10b** 18 (94 : 6)
9		(±)-**11a** 35 (83 : 17)	(±)-**11b** 60 (76 : 24)

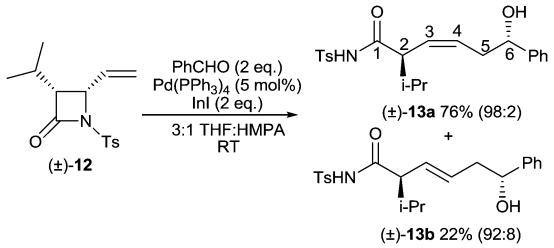
[a] Isolated yields. [b] Assayed by ^{1}H NMR integration. [c] Assayed by ^{1}H NMR integration of an inseparable mixture of (±)-**8a** and (±)-**8b**.

Is it worth noting that the presented reaction constitutes an example of a usually unfavourable α-allylation process where the addition of an allylmetal to a carbonyl group takes place on the less substituted carbon of the allyl system.[1,2] For instance, the observed regioselectivity stays in sharp contrast to the results of analogous reactions of 2-vinylaziridines, which under the same conditions afforded mainly 1,3-aminoalcohols, typical γ-allylation products.[2e,f]

Although the obtained result was quite encouraging, product distribution was not fully satisfactory. Therefore in the next step, the solvent effect on the reaction outcome was explored. At first, other common relatively polar ethers were tested. The use of anhydrous dioxane led to a similar yield and (*Z*)-selectivity but d.r. of predominant (3*Z*)-2,6-*anti*-enediol (±)-**3a** dropped significantly (Table 1, entry 2). Carrying out the reaction in anhydrous DME gave higher yield and better (*Z*)-selectivity but again the 2,6-*syn* : 2,6-*anti* ratio of both (3*Z*)- and (3*E*)-enediols suffered (Table 1, entry 3). When less polar solvents were applied (Et_2O, MTBE, toluene and DCM) only partial conversion (<50%) of the starting material was observed within several days, most likely due to poor solubility of the reagents. Surprisingly, the use of more polar, aprotic solvents (DMF and NMP) caused (*Z*)/(*E*)-selectivity reversal and in these cases (3*E*)-2,6-*anti*-enediol (±)-**3b** was isolated as the major product in good yield and with moderate (80 : 20) 2,6-*anti*-selectivity (Table 1, entries 4 and 5). Performing the reaction in MeOH resulted in the formation of a complex mixture of products, indicating that protic solvents are not suitable for the transformation (Table 1, entry 6). Since it has been reported that HMPA is often employed as a beneficial additive in Pd(0)/InI chemistry,[2c,g–i] several experiments using THF : HMPA mixtures in different proportions were carried out (Table 1, entries 7–10). As a result of this study it was established that a mixture of THF and HMPA in a 2 : 1 ratio gave the optimal result. Under these conditions, (3*Z*)-2,6-*anti*-enediol (±)-**3a** was obtained in 81% yield, with high (*Z*)-(84 : 16) and excellent 2,6-*anti*-(96 : 4) selectivity (Table 1, entry 9). The use of the 3 : 1 THF : HMPA mixture gave comparable results and it was used in the further investigation, as reducing the amount of HMPA is advantageous due to its high toxicity (Table 1, entry 8). Further reduction in the amount of HMPA led to a significant decrease of yield and (*Z*)/(*E*)-selectivity (Table 1, entry 7). Surprisingly, attempts to replace HMPA with less toxic DMPU resulted in the reversal of (*Z*)/(*E*)-selectivity and in this case (3*E*)-2,6-*anti*-enediol (±)-**3b** was isolated as the major product in 68% yield, with moderate (77 : 23) 2,6-*anti*-selectivity (Table 1, entry 10).

To further explore our methodology, a variety of aromatic and aliphatic aldehydes were subjected to optimized reaction conditions (Table 2). All of the reactions involving aromatic aldehydes, electron rich or deficient, including furfural, afforded (3*Z*)-2,6-*anti*-enediols as major products in 70–81% yield and with high 2,6-*anti*-selectivity (Table 2, entries 1–3 and 8). Reactions of aliphatic aldehydes usually proceeded with somewhat lower (*Z*)- but the same high 2,6-*anti*-selectivity (Table 2, entries 4–7). An exception is the reaction involving 3-methylbut-2-enal, resulting in the formation of (3*Z*)-2,6-*anti*-isomer (±)-**11a** as a minor product in 35% yield and moderate (83 : 17) 2,6-*anti*-selectivity (Table 2, entry 9). Interestingly, the use of highly sterically hindered pivalaldehyde had no effect on the reaction rate and selectivity (Table 2, entry 6). Also the application of 4-hydroxybutyric aldehyde containing an unprotected hydroxyl group (existing mainly in hemiacetal form) proved to be very successful, giving (±)-**9a** in 65% yield and excellent 2,6-*anti*-selectivity (Table 2, entry 7).

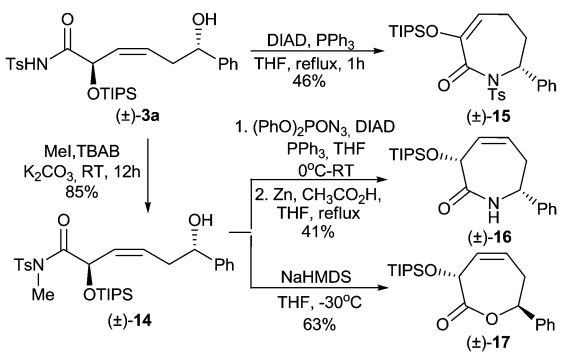
Next, a series of experiments were conducted using modified azetidin-2-ones to determine the effect of the β-lactam structure on the reaction outcome. Attempts of replacing the Ts group with common Boc and PMP protecting groups failed, as within



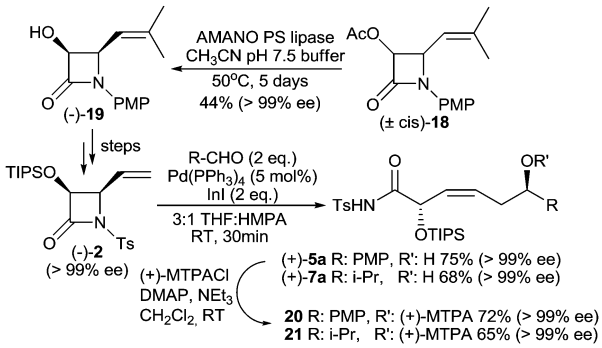
Scheme 2 $Pd(PPh_3)_4$/InI-mediated addition of *N*-Ts-3-iPr-azetidin-2-one (±)-**12** to benzaldehyde.

3 days no conversion was observed. These substrates appeared to be inert under optimized reaction conditions, indicating that a strongly electron withdrawing group attached to the nitrogen atom of β-lactam is necessary. Also the replacement of vinyl substituent with (*E*)-propenyl caused a dramatic drop in the reaction rate and only slight conversion (<5%) was observed within several days. However, the reaction of azetidin-2-one (±)-**12** containing the i-Pr substituent on C3 of the β-lactam ring proceeded smoothly to give (*Z*)-homoallylic alcohol (±)-**13a** as the major product in 76% yield and with excellent 2,6-*anti*-selectivity (Scheme 2).

Semi-protected 2,6-*anti*-enediols with internal (3*Z*)-substituted double bond and *N*-Ts-amide function could serve in the synthesis of a variety of linear derivatives and heterocycles of different ring sizes and substitution patterns. As a simple example of application of enediol (±)-**3a** in synthesis, chiral caprolactams (±)-**15**, (±)-**16** and caprolactone (±)-**17** were prepared using well-established methods (Scheme 3). Directly subjecting enediol (±)-**3a** to Mitsunobu conditions afforded *N*-Ts-lactam (±)-**15** as a single isomer in 46% yield. In the course of this transformation unexpected migration of a C=C double bond was observed, which was confirmed by NMR. Chemoselective methylation of the amide function of (±)-**3a** under PTC conditions giving (±)-**14** and subsequent cyclisation involving alkoxide generated *in situ* afforded lactone (±)-**17** in 63% yield. Lactam (±)-**16**, in turn, was prepared from (±)-**14** in two steps by the formation of an azide under Mitsunobu conditions and subsequent reduction with simultaneous cyclisation. Caprolactams and caprolactones constitute an important structural motif found in a range of natural products and their synthetic analogs exhibiting interesting pharmacological activities which make them highly desirable.[7]



Scheme 3 Application of (3*Z*)-2,6-*anti*-enediol (±)-**3a** in the synthesis of caprolactams (±)-**15**, (±)-**16** and caprolactone (±)-**17**.

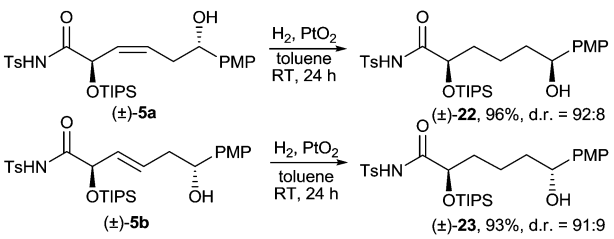


Scheme 4 Synthesis and $Pd(PPh_3)_4$/InI-mediated addition of enantioenriched β-lactam (−)-**2** to aldehydes.

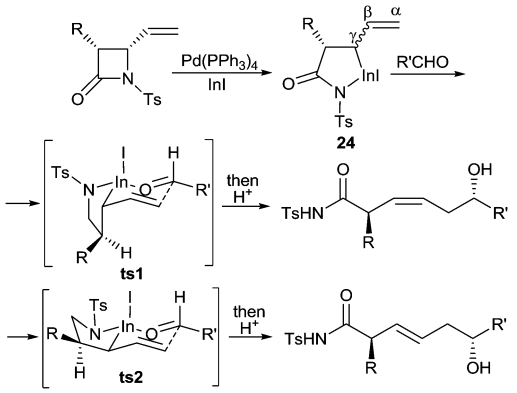
Finally, in order to verify that the method being developed may serve in asymmetric synthesis, enantioenriched 4-vinylazetidin-2-one (−)-**19** (>99% ee according to HPLC, see ESI†) was prepared from racemic acetyloxy-β-lactam (± *cis*)-**18** *via* lipase-catalysed kinetic resolution (Scheme 4).[8] Reactions of this compound with 4-methoxybenzaldehyde and isobutyric aldehyde gave the expected (*Z*)-2,6-*anti*-enediols (+)-**5a** and (+)-**7a** in good yield without any trace of racemisation, which was proven by the NMR study of Mosher's esters **20**, **21** (see ESI†).

Different methods were used to determine the configuration of the obtained (3*Z*)- and (3*E*)-2,6-*anti*-enediols **3a–11a**, **3b–11b** and homoallylic alcohols (±)-**13a** and (±)-**13b**. Their (*Z*)/(*E*)-configurations were easily assigned by analysis of coupling constants of the olefinic protons in ^{1}H NMR spectra ($J \sim 10$ Hz for (*Z*)- and $J \sim 15$ Hz for (*E*)-isomers). Also d.r.'s of all (3*Z*)- and (3*E*)-products were established using ^{1}H NMR spectroscopy. X-ray analysis of (±)-**5a** allowed us to establish its relative configuration as 2,6-*anti* (see ESI†). The configurations of other (3*Z*)-2,6-enediols were assigned by analogy. The relative configuration of (3*E*)-isomer (±)-**5b** was determined by the reduction of C=C double bonds of compounds (±)-**5a** and (±)-**5b** and by ^{1}H and ^{13}C NMR spectra comparison of obtained products (±)-**22** and (±)-**23**, which clearly showed that the predominant diastereoisomer of (±)-**5b** has an 2,6-*anti* configuration (Scheme 5). The configurations of other (3*E*)-2,6-enediols were assigned by analogy.

The mechanism of the transformations being investigated has not been studied and details are not clear. However, a plausible reaction pathway based on the observed regio- and stereoselectivity of the process is depicted in Scheme 6. The initial step consists of C4–N β-lactam bond cleavage by $Pd(PPh_3)_4$ followed by reductive transmetalation of the transient π-allylpalladium(II)



Scheme 5 Reduction of double bond of enediols (±)-**5a** and (±)-**5b**.



Scheme 6 Possible reaction pathway.

complex with InI, and subsequent fast isomerisation on the carbon atom attached to the metal. As a result of this sequence, the cyclic ε-amido-allylindium iodide **24**, in which the metal atom is situated in an overall unfavourable position γ as a consequence of coordination of indium to the amido group, is generated. Participation of this particular intermediate explains the observed regioselectivity resulting from a reaction on the usually unfavourable primary carbon of allyl system (position α), which is atypical for additions of allylindiums.[1,2] The addition step occurs *via* bicyclic, rigid transition states **ts1** and **ts2**, in which the group next to the indium adopts the axial or equatorial position, depending on conditions applied, leading, after subsequent protonation, to (3*Z*)- and (3*E*)-2,6-*anti*-enediols in different ratios, usually with high remote 1,5-asymmetric induction.

In summary, we have demonstrated the utility of readily available *N*-Ts-4-vinyloazetidin-2-ones as precursors of chiral ε-amido-allylindiums for the first time. Addition of these species to aldehydes proceeds with atypical regioselectivity for allylindium reagents and effective remote asymmetric induction to give semi-protected (3*Z*)- or (3*E*)-2,6-*anti*-enediols in high yield and, in the case of (3*Z*)-products, with excellent diastereoselectivity. When enantioenriched substrates were used, no racemisation was observed demonstrating that the developed methodology may be applied in asymmetric synthesis. The usefulness of obtained (3*Z*)-2,6-*anti*-enediols was exemplified in preparation of caprolactams and caprolactones. Further elaboration of the chemistry presented and its application in asymmetric synthesis of other types of heterocycles and selected natural products is currently in progress.

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