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Diastereoselective allylation of α-ketoamides bearing camphor *N*-tosylpyrazolidinone auxiliary: efficient synthesis of highly optically active two stereoisomers

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Abstract—Complementary allylation conditions were developed for the synthesis of both diastereomers of tertiary homoallylic alcohols. Treatment of camphor *N*-tosylpyrazolidinone derived α-ketoamides with allyltributylstannane afforded both the individual homoallylic alcohols in high optical purity (up to 98% de) when the reaction was carried out in the presence of $Sn(OTf)_2$ and $PdCl_2$, respectively. The stereochemical outcome and reversal of stereoselectivity in the reaction are proposed based on ^{13}C NMR and FTIR studies.

1. Introduction

The development of novel chiral auxiliaries that provide practical routes for the preparation of synthetically useful intermediates remains one of the most important fields in organic synthesis.[1] The fact that there are no universal chiral auxiliaries for all asymmetric transformations is a compelling reasons for discovering novel chiral auxiliaries for specific reactions.[2] From a practical synthetic point of view, the synthesis of both stereoisomers from the same chiral resources is attractive and has been a subject of considerable interest in recent years.[3] The reversal of stereochemistry from a single chiral starting material can be achieved by careful manipulation of the reaction components, especially the control of the architecture of the ligand-Lewis acid complex. The asymmetric allylation of ketones,[4] aldehydes[5] and imine[6] functionalities for the formation of homoallyl alcohols and homoallyl amines are well documented in the literature. The corresponding secondary and tertiary homoallylic alcohols are versatile intermediates that have been further used in organic synthesis.[7] However, allyl metal addition to α-keto esters and amides is a less well investigated topic.[8] Diastereoselective allylation of camphor *N*-phenylpyrazolidinone derived α-ketoamides was examined recently by us.[9] The corresponding quarternary α-hydroxy carbonyls were obtained with good to excellent stereoselectivity. However, to the best of our knowledge, a diastereoselective allylation of α-ketoamides with reversal of stereoselectivity has not been achieved to date. Here, we wish to report the asymmetric allylation of a novel camphor auxiliary derived α-ketoamides in the presence of a Lewis acid. The desired products were obtained in excellent diastereomeric excess in good to excellent chemical yields. The facial stereoselectivity and the stereochemical course of the reactions are discussed.

2. Results and discussion

The preparation of camphor *N*-tosylpyrazolidinone **4** followed the same synthetic route as described previously (Scheme 1).[2g] The treatment of (+)-ketopinic acid **1** with *p*-toluenesulfonhydrazide producing the desired hydrazone **2** in nearly quantitative chemical yield. Cyclization was carried out by treatment with $SOCl_2$ in EtOAc at 75 °C for 4 h. The corresponding C–N double bond was reduced with $NaCNBH_3$ in acetic acid to give the chiral camphor *N*-tosylpyrazolidinone **4** in 75% material yield. The desired α-ketoamides **5** are readily prepared by coupling the camphor *N*-tosylpyrazolidinone **4** with the freshly prepared α-ketocarboxylic acid chlorides at room temperature in 49–97% yields. It is noteworthy that both camphor *N*-tosylpyrazolidinone **4** and camphor *N*-tosylpyrazolidinone phenylglyoxylate **5a** exist as two structural conformers in the asymmetric unit as indicated by X-ray crystallographic analyses.[10] Two distinct *N*-invertomers of camphor *N*-tosylpyrazolidinone **4** were observed in which the tosyl group is oriented toward and away from the C7 dimethyl group (Scheme 1, the dihedral angles of $NNSC^2_{SP}$ are −72.0 and +84.1°, respectively).[11] On the other hand,

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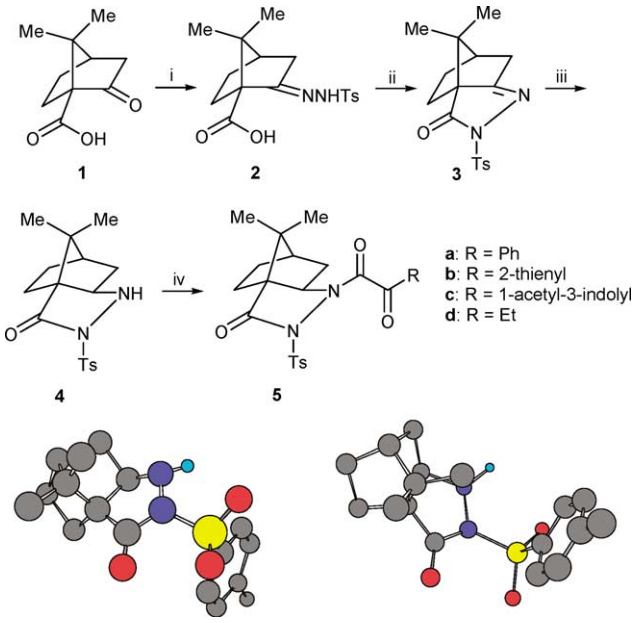


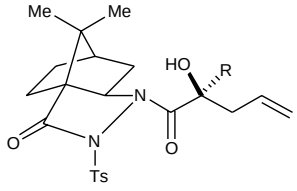
Scheme 1. Reagents and conditions: (i) *p*-toluenesulfonhydrazide, CH_2Cl_2, rt, 99%; (ii) $SOCl_2$, EtOAc, 75 °C, 90%; (iii) $NaCNBH_3$, AcOH, rt, 75%; (iv) RCOCOCl, CH_2Cl_2, base, rt, 49–97%.

the tosyl group points away from the C7 dimethyl group in **5a**, thus avoiding the electrostatic repulsion with the dicarbonyl groups (the dihedral angles of $NNSC^2_{SP}$ are −69.9 and −83.0°, respectively). In addition, the amide carbonyl group in **5a** is oriented away from the *N*-tosyl group with the dicarbonyl groups in an *s*-trans arrangement (the dihedral angles of COCO are 137.6 and 143.5°, respectively. See supporting information).

With the desired chiral α-ketoamides **5a–d** in hand, we examined the diastereoselective allylation. The camphor *N*-tosylpyrazolidinone phenylglyoxylate **5a** was chosen as a probe substrate. No reaction products were obtained when **5a** was treated with allyltributylstannane in the absence of a Lewis acid. Various metal triflates such as $Sc(OTf)_3$, $Sm(OTf)_3$, $Zn(OTf)_2$ and $Eu(OTf)_3$ were systematically screened, but resulted in either low to moderate chemical yields or a low level of diastereoselectivities (data not shown). A satisfactory result was obtained when the reaction was carried out in the presence of 2.0 equiv of $Yb(OTf)_3$ for 24 h (Table 1, entry 1). The stereoselectivity was further improved to an excellent level when $Sn(OTf)_2$ was employed in a 5 min reaction (entry 2). The diastereoselectivity was determined by ^{1}H NMR and HPLC studies of relevant peaks. The absolute stereochemistry of the newly generated stereogenic center in the major diasteoreomer **6a** was assigned to have an *R* configuration, deduced from the single crystal X-ray analysis. Interestingly, the sense of stereoinduction was reversed with less reactivity when the reaction was carried out in the presence of $PdCl_2$ and the structure of product **7a** was again confirmed by single crystal X-ray analysis (entry 3). A careful examination of the ^{1}H NMR spectra indicates that the characteristic C-2 methine proton (camphor numbering) appears at 3.16 ppm for the *R* isomer while at 4.32 ppm for the counter *S* isomer.[9,12] The diamagnetic anisotropy effect of the aromatic substituent may account for the shielding effect.

Having identified two discrete Lewis acids [$Sn(OTf)_2$ and $PdCl_2$] that can produce complementary diastereomers of the allylation reactions, we sought to examine the nature of the architecture of the chiral auxiliary backbone. Toward this end, the allylation proceeded smoothly when camphor *N*-tosylpyrazolidinone derived 2-thienylglyoxylate **5b** was used under the optimum reaction conditions, providing **6b** with excellent selectivity in the presence of $Sn(OTf)_2$ (entry 4). The opposite diasteoreomer with a similar selectivity was produced when $PdCl_2$ was used (entry 5).

Table 1. Diastereoselective allylation of camphor *N*-tosylpyrazolidinone derived α-ketoamides **5a–d** in the presence of a Lewis acid[a]



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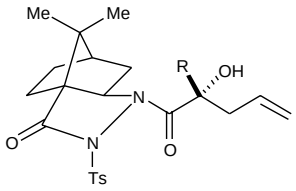

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Entry		R=	Lewis acid	*t*	Yield (%)[b]	Configuration[c]	Ratio (**6**:**7**)[d]
1	**5a**	Phenyl	$Yb(OTf)_3$	24 h	90	*R*	91:09
2	**5a**	Phenyl	$Sn(OTf)_2$	5 min	92	*R*	99:01
3	**5a**	Phenyl	$PdCl_2$	24 h	60	*S*	06:94
4	**5b**	2-Thienyl	$Sn(OTf)_2$	5 min	95	*S*	99:01
5	**5b**	2-Thienyl	$PdCl_2$	24 h	88	*R*	01:99
6	**5c**	1-Acetyl-3-indolyl	$Sn(OTf)_2$	5 min	98	*R*[f]	99:01
7	**5c**	1-Acetyl-3-indolyl	$PdCl_2$	24 h	—[e]	—	—
8	**5d**	Ethyl	$Sn(OTf)_2$	5 min	95	*S*	89:11
9	**5d**	Ethyl	$PdCl_2$	24 h	<10	*R*[f]	15:85

[a] Unless otherwise specified, all reactions were carried out in a solvent [in CH_3CN when $Sn(OTf)_2$ was used and in CH_2Cl_2 when $PdCl_2$ was used] at room temperature using **5** (0.11 mmol), allyltributylstannane (1.06 mmol) and a Lewis acid (0.22 mmol).
[b] Total isolated yield (**6**+**7**).
[c] The absolute stereochemistry of the newly generated stereogenic center was deduced by X-ray crystallographic analyses.
[d] Ratios of diastereomers were determined by ^{1}H NMR analysis of relevant peaks and HPLC analyses of crude products.
[e] The deacylated compound *N*-tosylcamphorpyrazolidinone-3-indoloylglyoxylate was isolated in 50%.
[f] Absolute stereochemistry are assigned by analogy.

It is noteworthy that, under either reaction conditions, no desired allylation product was observed with camphor *N*-tosylpyrazolidinone derived 3-indoloylglyoxylate. This was presumably due to the presence of an active hydrogen atom that decreases the reactivity. This problem was eliminated when NH protected analogue was used. Thus, camphor *N*-tosylpyrazolidinone-1-acetyl-3-indoloylglyoxylate **5c** upon allylation afforded the expected product with fairly high yield and selectivity in the presence of $Sn(OTf)_2$ (entry 6). However, no desired reaction products were observed when $PdCl_2$ was employed and the deacylation product was isolated (entry 7). Finally, the aliphatic substrate **5d** efficiently participates in the reaction, leading to the desired products with good diastereoselectivity, but the reactivity decreased dramatically when $PdCl_2$ was used as a Lewis acid (entries 8–9).

The high degree of stereoselectivity and the reversal of stereoselectivity can be rationalized by the chelation and non-chelation control of the Lewis acid with α-ketoamides **5** as shown in Figure 1. Among the possible conformations, the pseudo planar *s*-trans conformer of the α-dicarbonyl group in **5** is electronically favored over its *s*-cis conformer to avoid electrostatic repulsive interactions between the adjacent carbonyl groups. This was confirmed by X-ray crystallographic analyses of **5a**,**b** in the solid states. The reversal of stereoselectivity can be explained by simple ^{13}C NMR and FTIR studies. When a mixture of $Sn(OTf)_2$ and **5a** in CD_3CN was examined by ^{13}C NMR, no significant chemical shift difference in the carbonyl region was observed (<0.05 ppm) in comparison with a spectrum of the pure substrate.[13] This indicates that there is little chelation of Lewis acid metal atom with the carbonyl oxygen atoms. In addition, no significant carbonyl group stretching band changes in the infrared spectrum of the mixture were observed. However, a new stretching band corresponding to an S=O group developed at 1272 cm^{-1}, which is different from the stretching band of 1240 cm^{-1} in **5a**.[14] On the other hand, a mixture of $PdCl_2$ and substrate **5a** give no significant carbonyl signal shift difference or absorption band changes (carbonyl and sulfonyl groups) by ^{13}C NMR and FTIR spectroscopy. These data indicate a strong coordination of the $Sn(OTf)_2$ with sulfonyl oxygen atoms and this may account for the much faster reaction in the presence of $Sn(OTf)_2$ in comparison to the use of $PdCl_2$ (5 min vs 24 h). The coordination of the tin to the sulfonyl group resulted in the rapid release of the nucleophilic allyl group. The allyl group then attacks the α-carbonyl amide group from the bottom *si* face to afford the desired product.

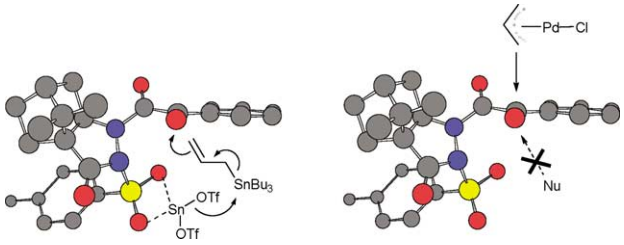

Figure 1. Proposed mechanistic explanation of the diastereoselective allylation. The stereoview of the Chem3D structure of **5a** was generated from the X-ray crystal coordinates. All hydrogen atoms are omitted for the sake of clarity.

While, in the case of $PdCl_2$, the electronic rich tosyl group prevents nucleophilic addition from the *si* face, leading to the addition from the top *re* face.[15]

3. Conclusion

In conclusion, a new camphor-based chiral auxiliary *N*-tosylpyrazolidinone was synthesized, and tested as a stereocontrolling element in allylation reactions across a range of substrates. The present work confirms that the correct choice of Lewis acid is essential in determining the diastereoselective outcome of the allylation.[16] The strongly chelating $Sn(OTf)_2$ led to the *si* face addition diastereomer, while the non-chelating $PdCl_2$ gave the counter diastereomer with allyltributyltin. Further synthetic applications are currently underway.

4. Experimental

4.1. General methods

All reagents were used as purchased from the commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^1H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^1H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrum 500 spectrometer. Only the characteristic peaks are quoted. EI mass spectra were recorded on Finnigan TSQ-700 at an ionizing energy of 70 eV and HRMS spectra were recorded on JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Analytical high-performance liquid chromatography was performed on a JASCO PU-1580 HPLC (ZORBAX analytical NH_2 column). Solutions were evaporated to dryness under reduced pressure with a rotary evaporator and the residue was purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated the deposit numbers CCDC 281384-281390, and 284467.[17]

4.1.1. 2-(2-Tosylhydrazono)-7,7-dimethylbicyclo[2.2.1]-heptane-1-carboxylic acid (2). To a solution of (+)-ketopinic acid **1** (20 g, 109.9 mmol) in CH_2Cl_2 (300 mL) was added *p*-toluenesulfonhydrazide (22.5 g, 120.9 mmol) in one portion and the mixture was allowed to stir for 4 h at room temperature. The reaction mixture was diluted with water (500 mL) and extracted with dichloromethane (3×500 mL), the organic layer was separated and dried over anhydrous $MgSO_4$ and concentrated to give ketopinic acid tosylhydrazone **2** as a white solid (38.1 g; 99%); mp: 114–115 °C. $R_f=0.29$ (1:1 hexanes/EtOAc). $[\alpha]_D^{27}$ +47.1

(*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, $J=7.6$ Hz), 7.74 (br s, 1H, –NH–, D_2O exchangeable), 7.35 (d, 2H, $J=7.6$ Hz), 2.51–2.39 (m, 2H), 2.43 (s, 3H), 2.09–2.03 (m, 2H), 1.94 (d, 1H, $J=17.4$ Hz), 1.68–1.62 (m, 1H), 1.33–1.28 (m, 1H), 1.20 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.0, 145.0, 134.3, 130.1, 127.9, 61.1, 51.7, 44.3, 33.9, 31.1, 27.5, 21.5, 19.7, 18.3; IR (neat, cm^{-1}): 3436–2408 (br), 1715, 1597, 1416, 1337, 1166, 1088, 920; HRMS (EI) calcd for $C_{17}H_{22}N_2O_4S$ 350.1295. Found 350.1283.

4.1.2. 10,10-Dimethyl-3-*N*-tosyl-4-aza-tricyclo[5.2.1.0^{1,5}]-dec-4-en-2-one (3). The above prepared ketopinic acid tosylhydrazone **2** (20 g, 57.14 mmol) was dissolved in ethyl acetate (300 mL). To this solution was added thionyl chloride (15.8 mL, 217.14 mmol) slowly and the reaction mixture was brought to reflux at 75 °C for 4 h under N_2 atmosphere. The reaction mixture quenched with water (600 mL) and extracted with ethyl acetate (3×600 mL). The dried $MgSO_4$ extract was concentrated in vacuo and purified by flash column chromatography, eluted with (1:1 hexanes/EtOAc) afforded the cyclized product **3** as a colorless solid (17.07 g; 90%).; mp: 83–84 °C. $R_f=0.44$ (1:1 hexanes/EtOAc). $[\alpha]_D^{27}$ −99.6 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J=7.9$ Hz), 7.32 (d, 2H, $J=7.9$ Hz), 2.59 (d, 1H, $J=18.0$ Hz), 2.43 (s, 3H), 2.22–2.20 (m, 2H), 2.15 (d, 1H, $J=18.0$ Hz), 2.10–2.05 (m, 1H), 1.76–1.69 (m, 1H), 1.52–1.45 (m, 1H), 1.12 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.2, 145.2, 135.3, 129.7, 127.9, 64.0, 50.9, 48.7, 32.2, 26.8, 26.0, 21.5, 18.5, 18.1; IR (neat, cm^{-1}): 3065, 2961, 2923, 2853, 1760, 1747, 1645, 1598, 1455, 1373, 1295, 1258, 1178, 1082, 959, 814, 705; HRMS (EI) calcd for $C_{17}H_{20}N_2O_3S$ 332.1189. Found 332.1190; Crystal data for **3** (colorless crystal, recrystallized from hexanes/EtOAc) at 25 °C: $C_{17}H_{20}N_2O_3S$, *M* 332.422, Orthorhombic, $P2_12_12_1$, $a=10.1101(2)$ Å, $b=12.9076(3)$ Å, $c=25.9674(8)$ Å, $V=3388.67(15)$ Å^3, $Z=8$, $D_x=1.303$ Mg/m^3, $\mu=0.21$ mm^{-1}, 2336 reflections, 416 parameters, $R=0.058$, $R_w=0.096$.

4.1.3. 10,10-Dimethyl-3-*N*-tosyl-4-aza-tricyclo[5.2.1.0^{1,5}]-decan-2-one (4). To a stirred solution of cyclized substrate **3** (5.05 g, 15.21 mmol) in AcOH (75 mL) at room temperature was added slowly $NaBH_3CN$ (13.19 g, 210 mmol). The reaction mixture was stirred at room temperature for 30 min until the reaction was completed and diluted with H_2O (750 mL) and extracted with CH_2Cl_2 (3×600 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a crude product, which is purified by flash column chromatography eluted with (2:1 hexanes/EtOAc) to yield **4** (3.75 g; 75%) as a white solid; mp: 118–119 °C. $R_f=0.38$ (2:1 hexanes/EtOAc). $[\alpha]_D^{27}$ +14.4 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J=8.0$ Hz), 7.32 (d, 2H, $J=8.0$ Hz), 5.05 (br s, 1H, –NH–), 3.5 (dd, 1H, $J=8.4$, 4.0 Hz), 2.44 (s, 3H), 2.11–2.02 (m, 2H), 1.89–1.80 (m, 2H), 1.66 (dd, 1H, $J=13.2$, 8.4 Hz), 1.26–1.15 (m, 2H), 0.94 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 145.2, 134.5, 129.4, 128.4, 64.5, 58.9, 52.5, 47.2, 36.4, 29.0, 26.4, 21.6, 20.4, 19.7; IR (neat, cm^{-1}): 3323, 3302, 2958, 2899, 1757, 1747, 1598, 1481, 1360, 1173, 1075, 863, 817; HRMS (EI) calcd for $C_{17}H_{22}N_2O_3S$ 334.1346. Found 334.1350. Anal. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38. Found: C, 61.07; H, 6.60; N, 8.20; Crystal data for **4** (colorless crystal, recrystallized from hexanes/EtOAc) at 25 °C: $C_{17}H_{22}N_2O_3S$, *M* 334.438, Monoclinic, $P2_1$, $a=9.7297(3)$ Å, $b=14.6999(4)$ Å, $c=12.2705(5)$ Å, $V=1714.77(10)$ Å^3, $Z=4$, $D_x=1.295$ Mg/m^3, $\mu=0.205$ mm^{-1}, 5864 reflections, 415 parameters, $R=0.0643$, $R_w=0.1547$.

4.2. General procedure for the synthesis of compounds 5a–c

Under N_2 atmosphere a mixture of benzoylformic acid (2.25 g, 15.0 mmol) and thionyl chloride (15.27 mL, 209.29 mmol) was refluxed at 75 °C for 2 h and concentrated on rotary evaporator to remove $SOCl_2$. The resulting crude mixture was dissolved in CH_2Cl_2 (15 mL) and added to a solution of camphor *N*-tosylpyrazolidinone **4** (1.0 g, 2.99 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stir for 15 min and quenched with water (50 mL) and extracted with CH_2Cl_2 (3×75 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated to give crude products, which were subject to flash column chromatography eluted with (2:1 hexanes/EtOAc) afforded the pure product **5a** (1.35 g, 97%) as a white solid.

4.2.1. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-(2-oxo-2-phenyl-acetyl)-tricyclo[5.2.1.0^{1,5}]decan-2-one (5a). $R_f=0.38$ (2:1 hexanes/EtOAc); mp: 179–181 °C. $[\alpha]_D^{27}$ −194.6 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H, $J=7.6$ Hz), 7.92 (s, 2H), 7.65 (t, 1H, $J=7.2$ Hz), 7.53 (t, 2H, $J=7.6$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 4.07 (s, 1H), 2.46 (s, 3H), 2.11 (t, 1H, $J=9.8$ Hz), 1.95–1.90 (m, 2H), 1.77 (dd, 1H, $J=13.4$, 8.2 Hz), 1.26 (s, 3H), 1.26–1.22 (m, 2H), 1.08 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 162.2, 146.0, 134.4, 133.6, 133.0, 130.5, 130.3, 130.0, 128.6, 128.4, 70.0, 60.0, 52.8, 47.5, 36.1, 28.8, 26.5, 21.6, 20.1, 20.0; IR (neat, cm^{-1}): 3065, 3003, 2964, 2925, 1768, 1680, 1652, 1594, 1483, 1450, 1385, 1241, 1173, 1083, 946, 816, 732; HRMS (EI) calcd for $C_{25}H_{26}N_2O_5S$ 466.1557. Found 466.1574. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00. Found: C, 64.33; H, 5.62; N, 5.75; Crystal data for **5a** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{25}H_{26}N_2O_5S$, *M* 466.54, Monoclinic, $P2_1$, $a=10.1710(5)$ Å, $b=11.8910(5)$ Å, $c=19.5700(12)$ Å, $V=2360.8(2)$ Å^3, $Z=4$, $D_x=1.313$ Mg/m^3, $\mu=0.176$ mm^{-1}, 7815 reflections, 596 parameters, $R=0.1298$, $R_w=0.1964$.

4.2.2. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[2-oxo-2-(thiophen-2-yl)acetyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (5b). White solid. $R_f=0.35$ (2:1 hexanes/EtOAc); mp: 180–182 °C. $[\alpha]_D^{27}$ −232.7 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, $J=3.6$ Hz), 7.93 (s, 2H), 7.81 (d, 1H, $J=4.4$ Hz), 7.37 (d, 2H, $J=8.0$ Hz), 7.2 (t, 1H, $J=4.4$ Hz), 4.11 (d, 1H, $J=6.8$ Hz), 2.46 (s, 3H), 2.09–2.06 (m, 1H), 1.94–1.92 (m, 2H), 1.82 (dd, 1H, $J=14.0$, 8.4 Hz), 1.26–1.22 (m, 2H), 1.18 (s, 3H), 1.05 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 174.3, 161.4, 146.0, 139.5, 137.0, 134.6, 129.8, 129.1, 128.9, 128.7, 70.5, 60.3, 52.6, 47.4, 36.8, 28.8, 26.7, 21.8, 20.3, 20.0; IR (neat, cm^{-1}): 3106, 2997, 2962, 2920, 2884, 1766, 1652, 1596, 1409, 1380, 1357, 1246, 1175, 1083, 1055, 815; HRMS (EI) calcd for $C_{23}H_{24}N_2O_5S_2$ 472.1127. Found 472.1129. Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.45; H, 5.12; N, 5.93. Found:

C, 58.68; H, 5.11; N, 5.88; Crystal data for **5b** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{23}H_{24}N_2O_5S_2$, M 472.56, Monoclinic, $P2_1$, a=12.5900(4) Å, b=6.6550(2) Å, c=13.2260(5) Å, V=1107.62(6) Å^3, Z=2, D_x=1.417 Mg/m^3, μ=0.279 mm^{-1}, 3697 reflections, 285 parameters, R=0.0735, R_w=0.1837.

4.2.3. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[2-(1-acetyl-1*H*-indol-3-yl)-2-oxoacetyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (5c). White solid. R_f=0.59 (2:1 hexanes/EtOAc); mp: 194–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.49–8.47 (m, 1H), 8.36–8.34 (m, 1H), 7.94 (s, 2H), 7.48–7.42 (m, 2H), 7.36 (d, 2H, J=7.6 Hz), 4.22 (s, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 2.12 (td, 1H, J=11.7, 3.9 Hz), 1.96–1.93 (m, 2H), 1.86 (dd, 1H, J=13.7, 8.0 Hz), 1.31–1.24 (m, 3H), 1.21 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 169.0, 162.2, 146.1, 136.2, 135.9, 129.8, 129.0, 127.1, 126.7, 125.6, 122.0, 117.7, 116.6, 70.7, 60.4, 52.7, 47.6, 29.7, 28.9, 26.7, 23.9, 21.8, 20.3, 20.1; IR (neat, cm^{-1}): 3059, 2962, 2925, 1768, 1732, 1652, 1539, 1448, 1379, 1212, 1175, 1008, 756; HRMS (EI) calcd for $C_{29}H_{29}N_3O_6S$ 547.1777. Found 547.1779.

4.2.4. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-(2-oxobutanoyl)-tricyclo[5.2.1.0^{1,5}]decan-2-one (5d). Under N_2 atmosphere a mixture of 2-ketobutyric acid (3.00 g, 29.30 mmol) and thionyl chloride (32.1 mL, 440.7 mmol) was refluxed at 75 °C for 2 h and concentrated on rotary evaporator to remove $SOCl_2$. The resulting crude product was dissolved in CH_2Cl_2 (5 mL) and added to a solution of camphor *N*-tosylpyrazolidinone **4** (0.20 g, 0.59 mmol) in CH_2Cl_2 (5 mL). This was added pyridine (2.30 mL, 29.50 mmol) and the reaction was allowed to stir at room temperature for 12 h. The reaction mixture was then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts dried over anhydrous $MgSO_4$ and the crude products were purified by flash column chromatography eluted with (2:1 hexane/EtOAc) provided product **5d** (0.12 g; 50%) as a colorless oil. R_f=0.38 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 2H, J=8.2 Hz), 7.40 (d, 2H, J=8.2 Hz), 3.78 (m, 1H), 3.11 (dq, 1H, J=19.0, 7.2 Hz), 2.81 (dq, 1H, J=19.0, 7.2 Hz), 2.48 (s, 3H), 2.03–1.86 (m, 4H), 1.81 (dd, 1H, J=14.3, 8.2 Hz), 1.26–1.20 (m, 2H), 1.16 (t, 3H, J=7.2 Hz), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 174.9, 162.3, 146.4, 133.9, 130.0, 128.6, 70.3, 60.0, 52.4, 47.3, 35.2, 31.7, 28.7, 26.6, 21.6, 20.2, 19.8, 6.9; IR (neat, cm^{-1}): 2964, 2941, 2889, 1769, 1726, 1660, 1596, 1458, 1379, 1189, 1175, 1086, 964, 815; HRMS (EI) calcd for $C_{21}H_{26}N_2O_5S$ 418.1562. Found 418.1560.

4.3. Typical procedure for the synthesis of compounds 6a and 7a

To a solution of camphor *N*-tosylpyrazolidinone derived α-ketoamide (51.27 mg, 0.11 mmol) in CH_3CN (4 mL) was added allyltributylstannane (0.37 mL, 1.06 mmol) and tin(II) triflate (91.7 mg, 0.22 mmol). The reaction was allowed to stir for 5 min at room temperature. The mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layers were separated and dried over anhydrous $MgSO_4$ and concentrated to give crude products. Further purificatin by flash column chromatography eluted with (3:1 hexanes/EtOAc) afforded **6a** and **7a** as a white solid (51.42 mg; 92%, ratio of diastereomers 99:01).

4.3.1. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-hydroxy-2-phenylpent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6a). R_f=0.54 (2:1 hexanes/EtOAc); mp: 170–172 °C. $[\alpha]_D^{27}$ +142.0 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, J=8.0 Hz), 7.54 (d, 2H, J=7.2 Hz), 7.37 (d, 2H, J=8.0 Hz), 7.33–7.26 (m, 3H), 5.92 (m, 1H), 5.35 (d, 1H, J=9.6 Hz), 5.28 (d, 1H, J=16.8 Hz), 3.34 (dd, 1H, J=13.2, 5.5 Hz), 3.16 (s, 1H), 3.02 (s, 1H), 2.76–2.73 (m, 1H), 2.46 (s, 3H), 2.46–2.42 (m, 1H), 2.00–1.94 (m, 1H), 1.81–1.78 (m, 3H), 1.27 (s, 3H), 1.05 (s, 3H), 0.97–0.91 (m, 1H), 0.86–0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 153.0, 144.8, 139.5, 136.0, 132.6, 129.3, 129.1, 128.4, 128.0, 124.7, 122.1, 78.4, 67.5, 59.0, 55.1, 49.5, 46.3, 41.5, 28.0, 26.2, 21.7, 20.7, 19.7; IR (neat, cm^{-1}): 3530, 3065, 2965, 2884, 1748, 1703, 1450, 1368, 1173, 1083, 814, 739; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 509.2060. Found 509.2053; Crystal data for **6a** (colorless crystal, recrystallized from hexanes/EtOAc) at 20 °C: $C_{28}H_{32}N_2O_5S$, M 508.62, Monoclinic, $P2_1$, a=8.6460(2) Å, b=11.5040(3) Å, c=13.4890(3) Å, V=1301.10(5) Å^3, Z=2, D_x=1.298 Mg/m^3, μ=0.165 mm^{-1}, 4476 reflections, 326 parameters, R=0.0652, R_w=0.1377.

4.3.2. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-hydroxy-2-phenylpent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (7a). White solid. R_f=0.46 (2:1 hexanes/EtOAc); mp: 194–195 °C. $[\alpha]_D^{27}$ −71.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H, J=7.8 Hz), 7.67 (d, 2H, J=7.8 Hz), 7.39–7.28 (m, 5H), 5.94 (m, 1H), 5.32 (d, 1H, J=10.1 Hz), 5.26 (d, 1H, J=17.2 Hz), 4.32 (t, 1H, J=6.2 Hz), 3.27 (dd, 1H, J=13.4, 6.2 Hz), 2.93 (br s, 1H), 2.66 (dd, 1H, J=13.4, 8.4 Hz), 2.46 (s, 3H), 2.08–2.02 (m, 1H), 1.89–1.74 (m, 3H), 1.56 (s, 1H), 1.27–1.16 (m, 2H), 0.90 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.9, 145.2, 140.2, 135.6, 133.0, 129.5, 128.9, 128.1, 127.6, 125.4, 121.9, 78.7, 72.5, 60.3, 51.7, 51.1, 47.0, 39.5, 29.1, 26.5, 21.8, 20.2, 19.5; IR (neat, cm^{-1}): 3504, 3065, 2965, 2935, 1755, 1668, 1447, 1379, 1295, 1189, 1174, 1086; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 508.2026. Found 508.2009; Crystal data for **7a** (colorless crystal, recrystallized from hexanes/EtOAc) at −73 °C: $C_{28}H_{32}N_2O_5S$, M 508.62, Orthorhombic, $P2_12_12_1$, a=6.3790(2) Å, b=18.5760(6) Å, c=21.1690(8) Å, V=2508.45(15) Å^3, Z=4, D_x=1.347 Mg/m^3, μ=0.172 mm^{-1}, 4409 reflections, 326 parameters, R=0.1054, R_w=0.1766.

4.3.3. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-hydroxy-2-(thiophen-2-yl)pent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6b). White solid. R_f=0.51 (2:1 hexanes/EtOAc); mp: 163–165 °C. $[\alpha]_D^{27}$ +122.8 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 2H, J=8.0 Hz), 7.35 (d, 2H, J=8.0 Hz), 7.20 (d, 1H, J=4.8 Hz), 7.01 (d, 1H, J=3.7 Hz), 6.92 (t, 1H, J=4.8 Hz), 5.89 (m, 1H), 5.36 (d, 1H, J=10.1 Hz), 5.31 (d, 1H, J=17.2 Hz), 3.52 (s, 1H), 3.35 (dd, 1H, J=13.3, 5.1 Hz), 3.25 (br s, 1H), 2.72–2.65 (m, 2H), 2.44 (s, 3H), 2.06–1.98 (m, 2H), 1.87–1.81 (m, 2H), 1.25 (s, 3H), 1.12–1.06 (m, 1H), 1.06 (s, 3H), 0.97 (t, 1H, J=10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 171.8, 144.9, 144.3, 135.8, 132.0, 129.2, 129.1, 127.3, 125.0,

124.2, 122.4, 78.0, 68.2, 59.0, 55.1, 49.7, 46.3, 41.7, 28.0, 26.2, 21.7, 20.6, 19.7; IR (neat, cm^{-1}): 3516, 2992, 2966, 2884, 1748, 1698, 1452, 1368, 1207, 1173, 1086, 815; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5S_2$ 514.1591. Found 514.1599; Crystal data for **6b** (colorless crystal, recrystallized from hexanes/EtOAc) at −123 °C: $C_{26}H_{30}N_2O_5S_2$, M 514.64, Monoclinic, $P2_1$, $a=8.5300(3)$ Å, $b=11.2470(4)$ Å, $c=13.4740(7)$ Å, $V=1247.57(9)$ Å^3, $Z=2$, $D_x=1.370$ Mg/m^3, $\mu=0.254$ mm^{-1}, 4278 reflections, 317 parameters, $R=0.0625$, $R_w=0.1386$.

4.3.4. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-hydroxy-2-(thiophen-2-yl)pent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (7b). White solid. $R_f=0.41$ (2:1 hexanes/EtOAc); mp: 167–168 °C. $[\alpha]_D^{27}$ −50.1 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2H, $J=8.2$ Hz), 7.37 (d, 2H, $J=8.2$ Hz), 7.25 (dd, 1H, $J=5.0$, 1.0 Hz), 7.17 (dd, 1H, $J=3.5$, 1.0 Hz), 6.95 (dd, 1H, $J=5.0$, 3.5 Hz), 5.95 (m, 1H), 5.34 (d, 1H, $J=10.8$ Hz), 5.30 (d, 1H, $J=18.0$ Hz), 4.34 (s, 1H), 3.25 (dd, 1H, $J=13.6$, 7.5 Hz), 3.18 (br s, 1H), 2.89 (dd, 1H, $J=13.6$, 7.5 Hz), 2.46 (s, 3H), 2.19–2.16 (m, 1H), 2.09–2.04 (m, 1H), 1.92 (dd, 1H, $J=14.4$, 8.1 Hz), 1.87–1.81 (m, 1H), 1.67 (t, 1H, $J=3.7$ Hz), 1.30–1.19 (m, 2H), 0.94 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.8, 145.3, 144.5, 135.4, 132.4, 129.5, 128.9, 126.8, 125.3, 124.4, 122.3, 78.3, 72.8, 60.4, 51.7, 51.5, 47.0, 39.9, 29.1, 26.6, 21.8, 20.3, 19.5; IR (neat, cm^{-1}): 3501, 3054, 2992, 2961, 1741, 1683, 1380, 1175, 1080, 1039, 936, 827, 752; HRMS (EI) calcd for $C_{26}H_{30}N_2O_5S_2$ 514.1591. Found 514.1598. Anal. Calcd for $C_{26}H_{30}N_2O_5S_2$: C, 60.68; H, 5.88; N, 5.44. Found: C, 60.82; H, 5.85; N, 5.45; Crystal data for **7b** (colorless crystal, recrystallized from hexanes/EtOAc) at −73 °C: $C_{26}H_{30}N_2O_5S_2$, M 514.64, Orthorhombic, $P2_12_12_1$, $a=9.8170(2)$ Å, $b=12.1720(2)$ Å, $c=21.7010(5)$ Å, $V=2593.11(9)$ Å^3, $Z=4$, $D_x=1.318$ Mg/m^3, $\mu=0.244$ mm^{-1}, 4469 reflections, 316 parameters, $R=0.0531$, $R_w=0.1272$.

4.3.5. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*R*)-2-(1-acetyl-1*H*-indol-3-yl)-2-hydroxypent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]-decan-2-one (6c). White solid. $R_f=0.60$ (2:1 hexanes/EtOAc); mp: 153–155 °C. $[\alpha]_D^{16}$ +157.3 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (d, 1H, $J=7.9$ Hz), 8.10 (d, 2H, $J=8.2$ Hz), 7.96 (d, 1H, $J=7.9$ Hz), 7.49 (s, 1H), 7.38 (d, 2H, $J=8.2$ Hz), 7.35 (t, 1H, $J=7.9$ Hz), 7.26 (t, 1H, $J=7.9$ Hz), 5.94 (m, 1H), 5.35 (d, 1H, $J=10.4$ Hz), 5.30 (d, 1H, $J=17.4$ Hz), 3.54 (dd, 1H, $J=7.7$, 5.1 Hz), 3.43 (dd, 1H, $J=12.6$, 4.1 Hz), 3.25 (br s, 1H), 2.80–2.75 (m, 1H), 2.69 (d, 1H, $J=12.6$ Hz), 2.61 (s, 3H), 2.47 (s, 3H), 1.98 (td, 1H, $J=12.0$, 4.8 Hz), 1.83–1.78 (m, 3H), 1.30–1.26 (m, 1H), 1.16 (s, 3H), 1.03 (s, 3H), 1.00–0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 172.2, 168.6, 145.2, 136.4, 135.5, 132.0, 129.3, 129.2, 127.3, 125.5, 123.8, 122.9, 122.1, 121.9, 121.7, 116.5, 77.4, 59.2, 47.4, 46.4, 41.2, 31.5, 28.1, 26.3, 22.6, 21.7, 20.5, 19.7, 14.1; IR (neat, cm^{-1}): 3418, 3080, 2962, 2930, 2894, 1748, 1710, 197, 1451, 1382, 1331, 1225, 1173, 1083, 815; HRMS (EI) calcd for $C_{32}H_{35}N_3O_6S$ 589.2247. Found 589.2240.

4.3.6. 10,10-Dimethyl-3-*N*-tosyl-4-*N*-[(*S*)-2-ethyl-2-hydroxypent-4-enoyl]-tricyclo[5.2.1.0^{1,5}]decan-2-one (6d). White solid. $R_f=0.42$ (2:1 hexanes/EtOAc); mp: 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 2H, $J=8.2$ Hz), 7.35 (d, 2H, $J=8.2$ Hz), 6.05 (m, 1H), 5.34 (d, 1H, $J=10.0$ Hz), 5.24 (d, 1H, $J=17.1$ Hz), 3.90 (s, 1H), 2.87 (dd, 1H, $J=13.3$, 5.2 Hz), 2.67–2.58 (m, 1H), 2.44 (s, 3H), 2.38–2.28 (m, 1H), 2.22–2.11 (m, 2H), 1.98–1.87 (m, 2H), 1.70–1.65 (m, 1H), 1.34 (s, 3H), 1.30–1.23 (m, 3H), 1.13 (s, 3H), 0.93 (t, 3H, $J=7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 144.8, 136.0, 132.7, 129.1, 129.0, 121.3, 78.5, 59.1, 46.2, 42.3, 32.1, 28.0, 27.8, 26.3, 21.7, 20.8, 19.8, 17.5, 13.6, 8.2; IR (neat, cm^{-1}): 3535, 2968, 2941, 2884, 1747, 1695, 1597, 1456, 1373, 1295, 1173, 1083, 814, 737; HRMS (EI) calcd for $C_{24}H_{32}N_2O_5S$ 460.2032. Found 460.2035.

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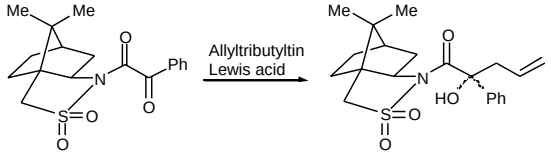
16. The diastereoselective allylation of the camphorsultam derived phenylglyoxylate was carried out under similar reaction conditions. The reversal of stereoselectivity was observed and the results are as follows.



$Sn(OTf)_2$: β-OH/α -OH = 13:87 (62%)
$Zn(OTf)_2$: β-OH/ α-OH = 86:14 (87%)

.
17. Compounds **3** (CCDC 284467), **4** (CCDC 281390), **5a** (CCDC 281384), **5b** (CCDC 281386), **6a** (CCDC 281385), **6b** (CCDC 281387), **7a** (CCDC 281388), **7b** (CCDC 281389). TOC.