Enantioselective Synthesis of [*b*]-Annulated Azepane Scaffolds

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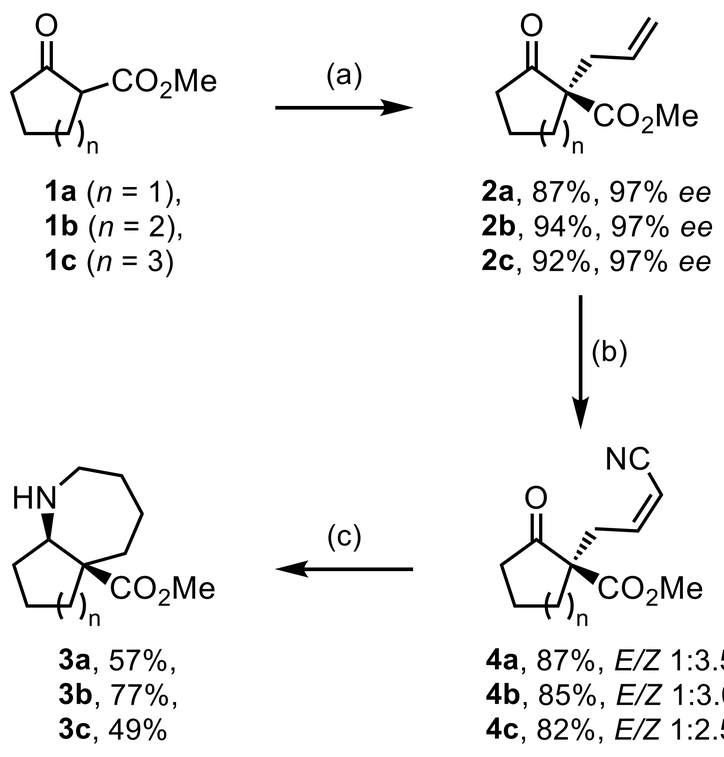
[*b*]-Annulated azepane scaffolds were synthesized by a three step sequence starting from commercially available β-oxoesters. Furthermore, optical activity was introduced by asymmetric allylic alkylation and it was retained throughout the sequence to yield the target motifs with >97% *ee*.

Asymmetric Synthesis

The enantioselective synthesis of [*b*]-annulated azepanes started with a Tsuji-Trost reaction following Yoshida's protocol:[1] β-oxoesters **1a-c** were asymetrically allylated to furnish the alkenes **2a-c** in good to excellent yields and >97% *ee* (Scheme 1). Olefin cross metathesis between alkenes **2a-c** and acrylonitrile afforded the unsaturated oxonitriles **4a-c** generally in high yields when the reaction was carried out in dilution (c = 0.05 mol/L). Catalytic hydrogenation using Pd/C at elevated pressures and temperatures led to the reductive cyclization and [*b*]-annulated azepanes **3a-c** were successfully obtained in moderate to good yields.



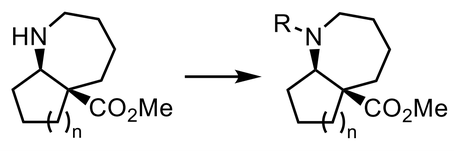
Scheme 1. (a) 1.1 eq. CH_2=$CHCH_2OH$, 5 mol% $Pd(OAc)_2$, 15 mol% $(4FC_6H_4)_3P$, 20 mol% *O*-TBDPS-L-Thr, PhMe, 40°C, 18 h; (b) 3 eq. CH_2=CHCN, 2 mol% Hoveyda-Grubbs 2nd gen. (in DCM), PhMe (0.05 mol/L); (c) H_2 (11 bar), 10% Pd/C, 5 eq. AcOH, MeOH, 80°C, 1 d.

The relative configurations for each ring size were confirmed by X-ray crystallography for different derivatives of azepanes **3a-c** and the corresponding ORTEP-representations are shown below.

Derivatization

In order to determine the degree of retention of optical activity, azepanes **3a-c** were trifluoroacetylated (entry 1) and analyzed by GC on a chiral phase revealing that no racemization occured throughout the synthetic sequence. Furthermore, various other acylations and alkylations were carried out to elucidate the scope of the azepane scaffold for derivatization (see Table 1).

Table 1: Amine functionalization.



#	*n*	R	conditions	Yield
1	1, 2, 3	CF_3CO	1.3 eq. TFAA, 1.3 eq. TEA, DCM, 40°C, 2 h	95–99%
2	1, 2, 3	Ac	1.5 eq. Ac_2O, 1.5 eq. TEA, DCM, 40°C, 2 h	98–100%
3	1, 2, 3	4-IC_6H_4CO	1.3 eq. 4-IC_6H_4COCl, 1.3 eq. TEA, DCM, 40°C, 4 h	79–99%
4	1, 2, 3	Boc	1.3 eq. Boc_2O, 1.3 eq. TEA, DCM, 40°C, 1–2 h	84–99%
5	1	$(NO_2)_2C_6H_3CO$	1.5 eq. 3,5-$(NO_2)_2C_6H_3COCl$, 1.5 eq. TEA, DCM, 40°C, 3 h	78%
6	1	Troc	1.3 eq. TrocCl, 2 eq. Py, DCM, 35°C, 20 h	96%
7	1	2,4,6-*i*$Pr_3C_6H_2SO_2$	1.5 eq. 2,4,6-*i*$Pr_3C_6H_2SO_2Cl$, 1.5 eq TEA, cat. DMAP, DCM, 35°C, 19 h	93%
8	2	ClC_6H_4NHCO	1.2 eq. 4-ClC_6H_4NCO, DCM, 40°C, 21 h	93%
9	2	Bros	1.9 eq. BrosCl, 2.7 eq. TEA, DCM, 40°C, 19 h	80%
10	2	*i*Bu	2 eq. *i*PrCHO, 1.5 eq. $NaCNBH_3$, 0.5 eq. $ZnCl_2$, MeOH, 23°C, 17 h	72%
11	2	2-$BrC_6H_4CH_2$	1.1 eq. 2-$BrC_6H_4CH_2Br$, 3 eq. K_2CO_3, MeCN, 24°C, 18 h	73%
12	2	*N*-Boc-β-Ala	1.2 eq. *N*-Boc-β-AlaOH, 1.2 eq. HATU, 1.2 eq. TEA, DCM, 50°C, 17 h	57%
13	3	4-$BrC_6H_4CH_2$	1.2 eq. 4-$BrC_6H_4CH_2Br$, 3 eq. K_2CO_3, 14 eq. TEA, MeCN, 50°C, 1 h	74%

ORTEP representations

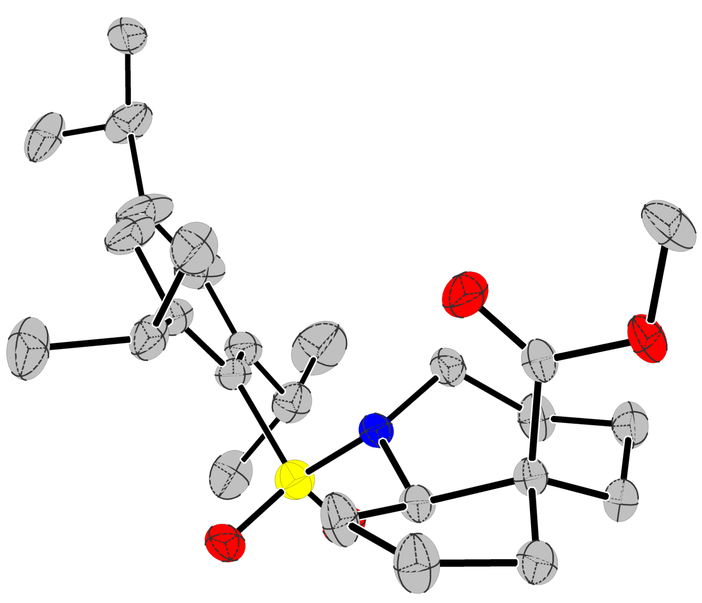


Table 1, **entry 9**

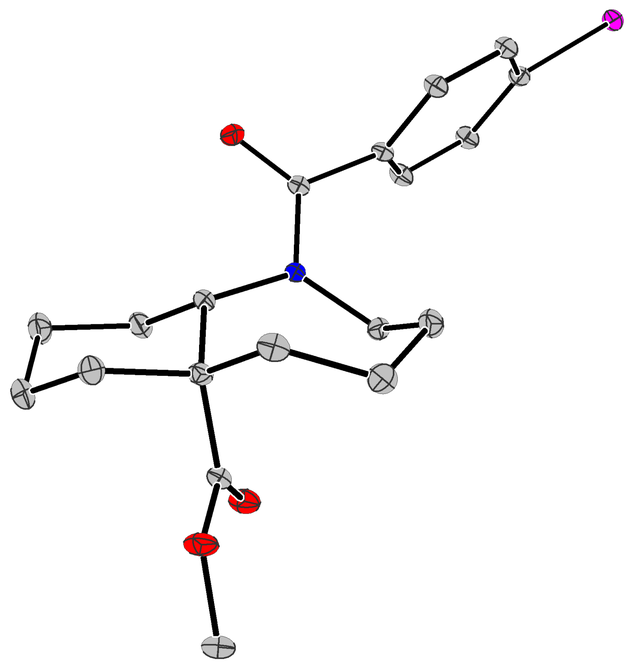


Table 1, **entry 3** (*n* = 2) from rac

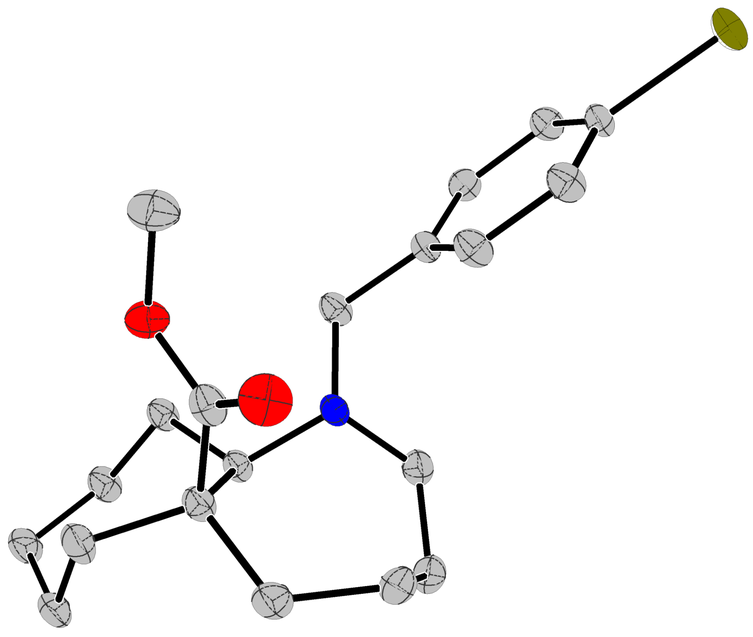


Table 1, **entry 13**

[1] M. Yoshida, *J. Org. Chem.* **2017**, *82*, 12821–12826.