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Synthesis of *N*-heterocyclic diols by diastereoselective pinacol coupling reactions

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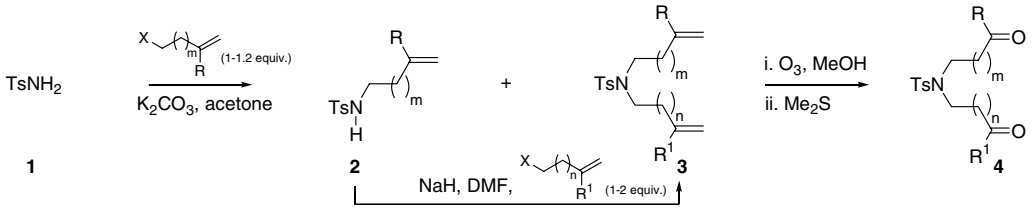
Abstract—A series of 5–8 membered *N*-heterocyclic diols have been prepared from acyclic dicarbonyls via diastereoselective pinacol reactions whereby *cis*- or *trans*-diol stereoselectivity is controlled by the choice of low-valent metal reagent used.

The pinacol coupling reaction has enjoyed a recent resurgence as a synthetic method due to the advent of a variety of low-valent metal reagents capable of affecting this transformation under mild reaction conditions and with excellent yields and stereoselectivities.[1] However, whilst the use of intramolecular pinacol couplings for the generation of carbocycles is well documented,[2] there are relatively few examples of the same reaction being applied to the synthesis of heterocyclic compounds. There are several reports of successful pinacol-type cyclisations of carbonyloxime and carbonylhydrazone precursors resulting in the formation of *N*-heterocyclic amino alcohols mediated by tributyltin hydride–AIBN or samarium diiodide.[3,4] However, to the best of our knowledge, there are no reported examples of the conversion of acyclic dicarbonyl compounds to the corresponding *N*-heterocyclic diols via an intramolecular pinacol cyclisation. This paper presents our initial results in this area.

The acyclic precursors required for our studies could be efficiently accessed from sulfonamide **1** by the route shown (Scheme 1). Thus alkylation of **1** under basic conditions generated mixtures of *mono*- **2a–c** and



1 2 3 4

a (m=n=0, R=R^1=Me)
b (m=n=1, R=R^1=H)
c (m=n=1, R=R^1=Me)
d (m=n=0, R=Me, R^1=H)
e (m=0, n=1, R=Me, R^1=H)
f (m=0, n=1, R=R^1=Me)
g (m=n=1, R=Me, R^1=H)
h (m=1, n=2, R=R^1=H)

2a (36%; X=Cl)
2b (61%; X=Br)
2c (32%; X=OTs)

3a (13%, from **1**)
3b (15%, from **1**)
3c (25%, from **1**)
3d (93%, from **2a**, X=Br)
3e (45%, from **2a**, X=Br)
3f (44%, from **2a**, X=OTs)
3g (70%, from **2c**, X=Br)
3h (86%, from **2b**, X=Br)

4a (64%)
4b (67%)
4c (96%)
4d (50%)
4e (78%)
4f (79%)
4g (72%)
4h (95%)

Scheme 1.

Keywords: Pinacol couplings; *N*-Heterocycles; Diols.
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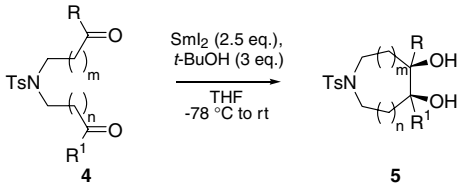
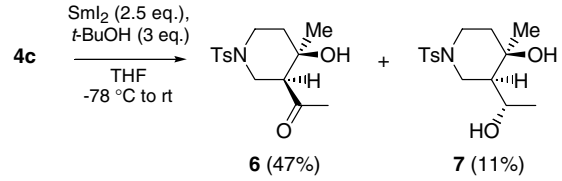


Scheme 2.

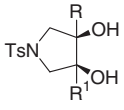
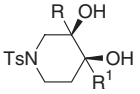
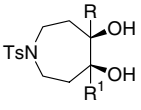
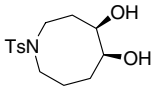


Scheme 3.

bis-alkylated **3a**–**c** sulfonamides, which were readily separated by column chromatography.[5] A second alkylation step then allowed preparation of a series of unsymmetrical dienes **3d**–**h** from **2a**–**c**. Subsequent ozonolysis of the dienes **3** followed by reductive work-up gave the requisite dicarbonyl compounds **4** in good to excellent yields after purification by chromatography.[6]

With the required precursors in hand we turned our attention to investigating the samarium diiodide-mediated pinacol coupling reaction of these systems (Scheme 2). Thus a THF solution (ca. 0.1 M) of the appropriate dicarbonyl compound **4a**–**h** and *t*-BuOH (3 equiv) was added dropwise to a solution of SmI_2 [ca. 0.1 M in THF, prepared[7] from Sm (3 equiv) and CH_2I_2 (2.5 equiv)] at −78 °C and the reaction allowed to warm to room temperature over 12 h. Work-up and chromatography resulted in the isolation of the corresponding diols **5a**–**h** in moderate to good yields (Table 1).[8] The stereochemical assignments of diols **5a**–**h** were made on the basis of NMR studies and X-ray crystallography for suitable solids.[9]

Table 1. Diols produced via Scheme 2

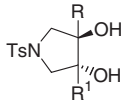
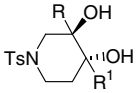
Entry	Dicarbonyl	Product diols **5** (overall yield)
		
1	**4a**	**5a** R = R^1 = Me (62%)
2	**4d**	**5d** R = Me, R^1 = H (50%)
		
3	**4e**	**5e** R = Me, R^1 = H (62%)
4	**4f**	**5f** R = R^1 = Me (73%)
		
5	**4b**	**5b** R = R^1 = H (37%; *cis*:*trans*, 4:1)[a]
6	**4g**	**5g** R = Me, R^1 = H (25%)
7	**4c**	**5c** R = R^1 = Me (0%—see text)
8	**4h**	
		5h (16%; *cis*:*trans*, 3:1)[a]

[a] Product ratios are calculated from ^{1}H and ^{13}C NMR. Only the *cis*-diols were isolated pure, 16% from **4b** and 10% from **4h**.

Pleasingly the SmI_2-mediated reactions were successful in furnishing pyrrolidines (entries 1–2) and piperidine-diols (entries 3–4) in good yields and with complete diastereoselectivity for the *cis*-diol. These results are comparable to those found with the corresponding carbocyclic systems.[2] Perhaps not surprisingly reactions to form seven- and eight-membered heterocycles (entries 5, 6 and 8) were less efficient and proceeded with lower levels of stereocontrol producing appreciable amounts of *trans*-diol (*cis*:*trans* ratios were determined from NMR analysis). However the *cis*-diols could be isolated pure from these reactions by careful chromatography. Interestingly reaction of diketone **4c** gave none of the anticipated diol (entry 7). Instead the two 6-membered heterocycles **6** (47%) and **7** (11%) were isolated from the reaction mixture as single diastereoisomers (Scheme 3, stereochemistry assigned by X-ray crystallography[9]). The formation of these unexpected products can be explained by an intramolecular aldol condensation of **4c** to produce ketone **6**, which is subsequently reduced stereoselectively by SmI_2 to the diol **7**. Catalysis of the aldol reaction may be facilitated by some Sm^{3+} species present in solution, however the reasons for the formation of these products in preference to the seven-membered diol are not clear.[10]

Having successfully completed the synthesis of a number of heterocyclic *cis*-diols we next turned our attention to accessing the corresponding *trans*-isomers. Itoh and co-workers have recently reported the use of Cp_2TiPh [generated in situ from $Cp_2Ti(Ph)Cl$ (3 mol%) and Zn (1 equiv)] as a catalyst for *trans*-selective intramolecular pinacol couplings to produce carbocyclic diols.[11] However there are no successful reports of the application of this reagent for the production of *N*-heterocycles. Indeed the failure of stoichiometric Cp_2TiPh to produce a hexahydroazepine from the pinacol-type coupling of an acylic carbonylhydrazone has been noted.[4] Reaction of a selection of dicarbonyl compounds **4** with 3 equiv of Cp_2TiPh (prepared by treatment of Cp_2TiCl_2 with *i*-PrMgCl and then PhMgBr)[12] in THF at room temperature for 12–18 h gave, after chromatography, the products indicated (Table 2).[13] It can be seen that this low-valent Ti^{3+} species successfully produces pyrrolidine and piperidine derived *trans*-diols (entries 1–4) from the corresponding acyclic precursors. Although levels of diastereoselectivity are not as high as in the SmI_2-mediated reaction the *trans*-diol could be isolated in pure

Table 2. Diols produced via reaction of **4** with Cp_2TiPh

Entry	Dicarbonyl	Product diols **8** (yield)
		
1	**4a**	**8a** R = R^1 = Me (64% + 5% *cis*-isomer **5a**)[a]
2	**4d**	**8d** R = Me, R^1 = H (59% + 18% *cis*-isomer **5d**)[a]
		
3	**4e**	**8e** R = Me, R^1 = H (37%)
4	**4f**	**8f** R = R^1 = Me (53% + 9% *cis*-isomer **5f**)[a]
5	**4b**	No identifiable products isolated
6	**4h**	No identifiable products isolated

[a] Stereoisomers were separated by column chromatography.

form and in moderate to good yields. The failure of the Cp_2TiPh reagent to furnish seven- and eight-membered rings (entries 5–6) is in accordance with the analogous reactions of carbonylhydrazones.[4]

In conclusion we have reported the first successful diastereoselective pinacol coupling reactions of dicarbonyl species to produce *N*-protected heterocyclic diols.[14] This synthetic route complements the alternative approach based on a ring closing metathesis-dihydroxylation strategy.[15] We are currently investigating both these approaches for the synthesis of more complex heterocycles.

Acknowledgements

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2. For selected examples see: (a) Carpintero, M.; Jaramillo, C.; Fernández-Mayoralas, A. *Eur. J. Org. Chem.* **2000**, 1285–1296; (b) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 6375–6381; (c) Storch de Gracia, I.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883–5889; (d) Kang, M.; Park, J.; Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 5528–5531; (e) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron. Lett.* **1991**, *32*, 1125–1128.
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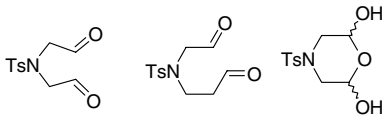
4. Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382–5390.
5. All new compounds gave satisfactory spectroscopic and microanalytical and/or HRMS analysis.
6. Attempts to prepare **3i** and **3j** via the route shown (Scheme 1) were unsuccessful due to the instability of these dials. In the case of **3i** only the hydrate **9** could be isolated



3i **3j** **9**

7. Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439–1445.
8. Selected spectroscopic data for *cis*-diols **5**:
5a: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.14$ (6H, s), 2.43 (3H, s), 3.31 (2H, d, *J* 10.2 Hz), 3.35 (2H, d, *J* 10.2 Hz), 7.32 (2H, d, *J* 8.0 Hz), 7.71 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.49$, 21.54, 57.86, 77.99, 127.45, 129.67, 133.87, 143.63.
5b: ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.71$–1.83 (2H, m), 1.98–2.12 (2H, m), 2.42 (3H, s), 3.18 (2H, ddd, *J* 13.5, 7.8 and 4.0 Hz), 3.41 (2H, ddd, *J* 13.5, 7.8 and 4.4 Hz), 3.95 (2H, dd, *J* 6.0 and 2.1 Hz), 7.30 (2H, d, *J* 8.0 Hz), 7.65 (2H, d, *J* 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) $\delta = 21.46$, 30.94, 42.08, 72.33, 126.97, 129.71, 135.65, 143.31.
5d: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.24$ (3H, s), 2.43 (3H, s), 3.16 (1H, dd, *J* 10.5 and 5.5 Hz), 3.26 (1H, d, *J* 10.5 Hz), 3.29 (1H, d, *J* 10.5 Hz), 3.59 (1H, dd, *J* 10.5 and 5.5 Hz), 3.81 (1H, app.t, *J* 5.5 Hz), 7.33 (2H, d, *J* 8.0 Hz), 7.70 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 21.55$, 23.04, 52.73, 57.16, 75.16, 76.16, 127.54, 129.71, 133.61, 143.72.
5e: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.30$ (3H, s), 1.79–1.86 (2H, m), 2.44 (3H, s), 2.69 (1H, d, *J* 11.8 Hz), 2.68–2.76 (1H, m), 3.05 (1H, dd, *J* 11.8 and 1.3 Hz), 3.30–3.38 (2H, m), 7.34 (2H, d, *J* 8.0 Hz), 7.64 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 21.52$, 22.88, 29.71, 43.54, 53.96, 69.89, 71.94, 127.64, 129.79, 132.99, 143.87.
5f: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.16$ (3H, s), 1.31 (3H, s), 1.77 (2H, dd, *J* 5.0 and 6.6 Hz), 2.44 (3H, s), 2.85 (1H, d, *J* 11.2 Hz), 2.94 (1H, dt, *J* 11.5 and 6.6 Hz), 3.03 (1H, dd, *J* 11.2 and 1.1 Hz), 3.15–3.20 (1H, m), 7.33 (2H, d, *J* 8.0 Hz), 7.63 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 21.31$, 21.47, 22.61, 35.72, 42.83, 53.16, 71.67, 72.39, 127.53, 129.71, 133.1, 143.67.
5g: ^{1}H NMR (400 MHz, CD_3OD) $\delta = 1.22$ (3H, s), 1.60 (1H, ddd, *J* 15.0, 8.0 and 3.5 Hz), 1.75 (1H, ddt, *J* 15.0, 7.8 and 3.0 Hz), 1.93–2.02 (2H, m), 2.45 (3H, s), 3.15 (1H, ddd, *J* 13.5, 8.0 and 3.0 Hz), 3.26 (1H, ddd, *J* 13.5, 8.0 and 3.0 Hz), 3.37–3.46 (2H, m), 3.47 (1H, dd, *J* 8.0 and 3.0 Hz), 7.41 (2H, d, *J* 8.0 Hz), 7.69 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, CD_3OD) $\delta = 20.44$, 25.41, 31.47, 36.68, 41.62, 42.17, 73.10, 75.79, 127.15, 129.83, 136.11, 143.83.
5h: ^{1}H NMR (250 MHz, CD_3OD) $\delta = 1.64$–2.05 (6H, m), 2.41 (3H, s), 2.71 (1H, ddd, *J* 13.7, 6.2 and 4.4 Hz), 2.81 (1H, ddd, *J* 13.9, 7.8 and 3.7 Hz), 3.41–3.56 (2H, m), 3.94 (1H, dt, *J* 8.5 and 3.0 Hz), 4.13 (1H, dt, *J* 8.5 and 3.0 Hz), 7.38 (2H, d, *J* 8.0 Hz), 7.65 (2H, d, *J* 8.0 Hz); ^{13}C NMR (62.9 MHz, CD_3OD) $\delta = 21.42$, 26.42, 30.78, 32.87, 46.10, 49.23, 73.53, 73.72, 128.21, 130.85, 136.67, 144.92.
9. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers: **5a**, CCDC 218780; **5h**, CCDC 218781; **6**, CCDC 218782; **7**, CCDC 218783. Copies of the data can be obtained, free of

charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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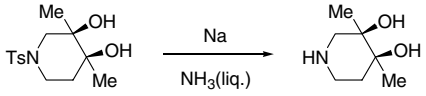
13. Selected spectroscopic data for *trans*-diols **8**:
8a: ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.23$ (6H, s), 1.51–1.68 (2H, br s), 2.42 (3H, s), 3.32 (2H, d, *J* 10.8 Hz), 3.47 (2H, d, *J* 10.8 Hz), 7.31 (2H, d, *J* 8.0 Hz), 7.73 (2H, d, *J* 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) $\delta = 17.58$, 21.51, 58.98, 79.94, 127.45, 129.64, 134.22, 143.53.
8d: ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.21$ (3H, s), 2.38 (3H, s), 3.18 (1H, d, *J* 10.5 Hz), 3.25 (1H, d, *J* 10.5 Hz), 3.12–3.25 (1H, m), 3.64 (1H, dd, *J* 10.5 and 4.6 Hz), 3.83–3.90 (1H, m), 7.28 (2H, d, *J* 8.0 Hz), 7.67 (2H, d, *J* 8.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) $\delta = 19.57$, 21.46, 54.39, 57.37, 76.84, 79.06, 127.42, 129.68, 133.56, 143.68.
8e: ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.29$ (3H, s), 1.61–1.74 (1H, m+2H, br s), 2.09 (1H, dd app.t, *J* 13.8 and 4.0 Hz), 2.45 (3H, s), 2.80 (1H, d, *J* 12.0 Hz), 2.95–3.06 (1H, m), 3.05 (1H, d, *J* 12.0 Hz), 3.07–3.17 (1H, m), 3.50 (1H, br s), 7.34 (2H, d, *J* 8.0 Hz), 7.65 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.77$, 21.51, 28.95, 42.65, 53.47, 70.69, 72.45, 127.62, 129.77, 132.99,143.81.
8f: ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 1.17$ (3H, s), 1.25 (3H, s), 1.47 (1H, d app.t, *J* 14.0 and 3.0 Hz), 1.58–1.68 (2H, br s) 2.07 (1H, ddd, *J* 14.0, 12.8 and 5.0 Hz), 2.44 (3H, s), 2.61 (1H, ddd, *J* 13.0, 12.8 and 3.0 Hz), 2.71 (1H, d, *J* 11.5 Hz), 3.29 (1H, dd, *J* 11.5 and 2.0 Hz), 3.52–3.61 (1H, m), 7.33 (2H, d, *J* 8.0 Hz), 7.64 (2H, d, *J* 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$+10% CD_3OD) $\delta = 19.40$, 21.31, 22.74, 34.68, 42.26, 52.78, 70.67, 71.50, 127.48, 129.68, 132.76, 143.79.
14. In preliminary experiments we have been able to efficiently remove the *p*-toluenesulfonyl protecting group using Na–NH_3(l), for example



5f 90%

15. For a recent example see: Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603–3607.