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Direct catalytic diastereoselective Mannich reactions: the synthesis of protected α-hydroxy-β-aminoketones

Nikki E. Stainforth [a], Gary A. Cutting [b], Matthew P. John [c], Michael C. Willis [a,*]

[a] *Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, UK*
[b] *Department of Chemistry, University of Bath, Bath BA2 7AY, UK*
[c] *Chemical Development Division, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK*

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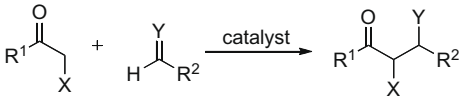
Dedicated to Professor George Fleet, an inspiring colleague, on the occasion of his 65th birthday

ABSTRACT

The combination of $Mg(ClO_4)_2$, 2,2′-bipyridine and *N*-methylmorpholine generates an effective catalyst system for the direct addition of α-carbonate-substituted ketones to aryl *N*-Ts imines. Methyl-carbonate-substituted ketones deliver acyclic α-hydroxy-β-aminoketone derivates, while ketones substituted with α-*iso*-propenyl-carbonates furnish cyclic carbamate adducts. In both cases the *anti*-configured Mannich products dominate.

1. Introduction

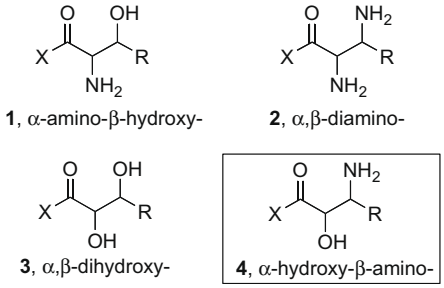
Stereodefined 1,2-aminoalcohols, together with the related 1,2-diols and 1,2-diamines, represent an important structural grouping that is found in many natural products and designed medicinal agents, and also feature heavily in a variety of ligands and auxillaries designed for asymmetric synthesis.[1] A useful strategy for the preparation of carbonyl-substituted variants of these systems is the combination of an α-oxygen- or α-nitrogen-functionalized enolate component with either an imine or an aldehyde, in aldol or Mannich processes, respectively. A more attractive version of these systems employs simple carbonyl derivatives, and not preformed enolates or enolate surrogates,[2] as the nucleophile component, in direct catalytic addition reactions (Eq. 1).[3]



(1)

X = OR, NR_2; Y = O, NR

We have recently shown that magnesium Lewis acid/tertiary amine base combinations generate effective catalyst systems for the direct combination of α-isothiocyanate-substituted nucleophiles with both aldehydes, to generate β-hydroxy-α-amino acid derivates **1**, or with imines, to deliver α,β-diamino acids **2** (Scheme 1).[4] We have also demonstrated that α-carbonate-substituted ketones undergo similar direct additions to aldehydes to provide α,β-dihydroxyketones **3**.[5] In this communication we demonstrate that the magnesium Lewis acid/tertiary amine-catalyzed addition of α-carbonate-substituted ketones to *N*-Ts-imines provides an efficient route to α-hydroxy-β-aminoketone products **4**, and in doing so establishes a common catalytic approach to all four of the 1,2-aminoalcohol combinations shown in Scheme 1.



Scheme 1.

2. Results and discussion

Our route for the preparation of α,β-dihydroxycarbonyl units is shown in Scheme 2, and features the direct addition of methyl carbonate-substituted ketones **5** to aryl aldehydes to deliver the corresponding cyclic carbonate derivates in good yields and with good selectivity for the *syn*-aldol products (*trans*-cyclic carbonates) **6**.[5] The high diastereoselectivity was attributed to the rapid cyclization of the *syn*-aldol adducts. Given the success of this system in accessing α,β-dihydroxycarbonyl systems we wished to extend the chemistry to the preparation of α-hydroxy-β-aminoketones by simply exchanging the aldehyde components for the corresponding imines (Eq. 2, Scheme 2).

* Corresponding author. Tel.: +44 1865 285126; fax: +44 1865 285002.
E-mail address: michael.willis@chem.ox.ac.uk (M.C. Willis).

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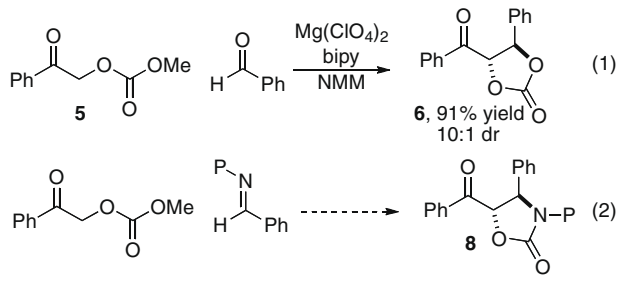
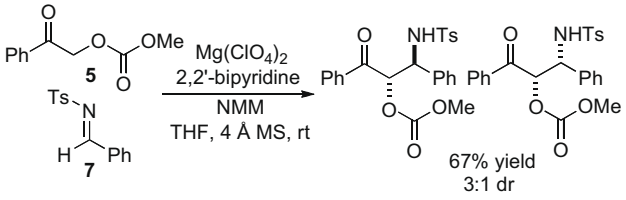


Scheme 2.

The reaction between methyl carbonate **5** and benzaldehyde-derived *N*-Ts-imine **7**, using the catalyst conditions optimized for the aldol process ($Mg(ClO_4)_2$, bipy, NMM), delivered a 67% yield of the desired *anti*- and *syn*-Mannich adducts in a 3:1 ratio (Scheme 3). None of the expected cyclic carbamate **8** was observed. Encouraged by this result we embarked on a brief optimization study. However, the use of alternative Lewis acids ($MgCl_2$, $Mg(OTf)_2$), bases (NEt_3, Hünigs base, DBU) or solvents (DCM, DME, 1,4-dioxane, toluene) failed to offer any improvements in terms of yield, diastereoselectivity, or for formation of the cyclic products. The original conditions involved combining 2 equiv of ketone with 1 equiv of imine; if this was varied to a 4:1 ratio the yield of the Mannich adducts could be increased to 80%. However, this small increase in yield was not considered sufficient to offset the greater quantity of ketone required.

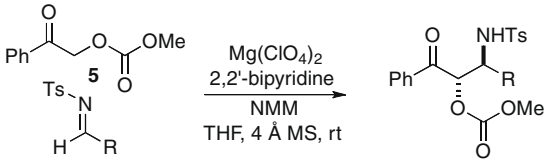


Scheme 3.

With optimized conditions in hand, we next explored the scope of the process with respect to the imine component (Table 1).[6] The first 15 entries in the Table all employ acetophenone-derived ketone **5**. The results presented in the Table demonstrate that a variety of both electron-rich and electron-poor aryl imines, featuring a range of functional groups, all perform well in the process. Imines featuring *para*-electron-donating groups deliver more selective reactions; for example, both the 4-OMe- and 4-^{t}Bu-substituted imines furnish the *anti*-Mannich adducts with 20:1 dr (entries 5 and 6). The thiophene- and furan-derived imines also perform well, again delivering adducts with good *anti*-selectivity (entries 13 and 14). The final entry demonstrates that variation of the nucleophile is also possible, with the 2-naphthyl-derived ketone (entry 16) delivering the expected adducts with similar yields and selectivities to the parent phenyl-derived system.

Our initial aim had been to develop a route to the cyclic carbamate adducts (**8**, Scheme 2). These were attractive targets as they represented internally protected versions of the original Mannich adducts. We were also interested in accessing the cyclic systems in order to probe the effect, if any, their formation would have on the overall diastereoselectivity of the process. In the event, we secured a route to the cyclic adducts by employing an alternative carbonate group on the ketone component. When *iso*propenyl-carbonate **9** was combined with the benzaldehyde-derived *N*-Ts-imine, using the standard reaction conditions, the corresponding cyclic carbamate adduct was isolated in 71% yield as a 20:1 mixture of diastereomers, with the *anti*-Mannich adduct (the *cis*-cyclic carbamate) dominating (Table 2, entry 1).[7] This compares favourably to the corresponding reaction with the methyl-carbonate nucleophile, which delivered the acyclic adducts as a 3:1 mixture of diastereomers in 67% yield (Table 1, entry 1). The *iso*propenyl-carbonate **9** was combined with three further imines, with the expected cyclic adducts being obtained in all cases, although the *para*-cyano-substituted imine displayed only a slight preference for the *anti*-adduct (7:3 dr, entry 3).

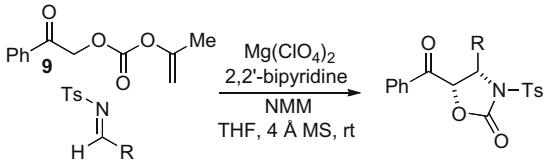
Table 1
Scope of the imine component[a]



Entry	Imine (R)	*anti:syn*[b]	Yield[c] (%)
1	Ph	3:1	67
2	2-Me–C_6H_4–	4:1	65
3	3-Me–C_6H_4–	5:1	75
4	4-Me–C_6H_4–	5:1	68
5	4-^{t}Bu–C_6H_4–	20:1	67
6	4-OMe–C_6H_4–	20:1	61
7	4-OPr–C_6H_4–	11:1	60
8	4-CN–C_6H_4–	3:1	62
9	4-Br–C_6H_4–	8:1	77
10	4-Cl–C_6H_4–	8:1	75
11	4-F–C_6H_4–	6:1	83
12	2-Naphthyl	4:1	69
13	3-Thienyl	20:1	67
14	2-Furyl	20:1	67
15	3-*N*-Piv-indolyl	8:1	43
16[d]	Ph	6:1	74

[a] Conditions: carbonate (2.0 equiv), *N*-Ts-imine (1.0 equiv), $Mg(ClO_4)_2$ (20 mol %), 2,2′-bipy (20 mol %), NMM (50 mol %), 4 Å MS, 24 h, THF, rt.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Isolated yield of combined diastereoisomers.
[d] 2-Naphthyl-derived ketone employed.

Table 2
Use of *iso*propenyl carbonate-substituted ketones[a]

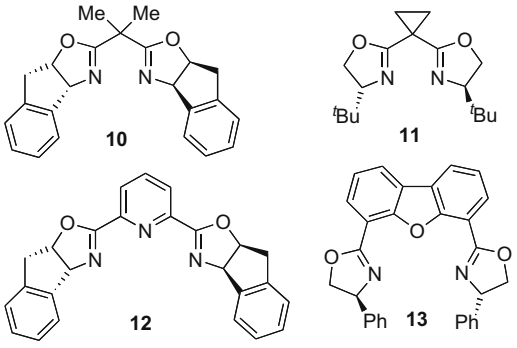


Entry	Imine (R)	*cis:trans*[b]	Yield[c] (%)
1	Ph	20:1	71
2	4-OMe–C_6H_4–	20:1	72
3	4-CN–C_6H_4–	7:3	61
4	3-Thienyl	20:1	64

[a] Conditions: carbonate (2.0 equiv), *N*-Ts-imine (1.0 equiv), $Mg(ClO_4)_2$ (20 mol %), 2,2′-bipy (20 mol %), NMM (50 mol %), 4 Å MS, 48 h, THF, rt.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Isolated yield of combined diastereoisomers.

Having established routes to both acyclic and cyclic α-hydroxy-β-aminoketone adducts, the stage was set to explore an enantioselective route. Given the catalyst system employed in the racemic series—$Mg(ClO_4)_2$, 2,2′-bipyridine, NMM—we were hopeful that exchange of the bipyridine ligand for an equivalent chiral variant would allow access to enantioenriched products. Unfortunately, evaluation of a number of bi- and tri-dentate N-based ligands, such

as the *bis*(oxazolines) **10** and **11**,[8] pyridine-*bis*(oxazoline) **12**[9] and furan-*bis*(oxazoline) **13**,[10] failed to generate an effective catalyst system, with only trace quantities (<5%) of the Mannich adducts being isolated (Scheme 4).



Scheme 4.

3. Conclusion

In conclusion, we have demonstrated that α-carbonate-functionalized ketones undergo direct addition to aryl *N*-Ts imines under the action of a $Mg(ClO_4)_2$/bipy/NMM catalyst system, to deliver α-hydroxy-β-aminoketone products. The use of methyl carbonate-substituted nucleophiles delivers acyclic adducts with moderate to good *anti*-selectivity. In contrast, the use of *iso*propenyl-substituted nucleophiles provides cyclic carbamate products, with generally good *anti*-Mannich diastereoselectivity. Good variation of the imine component was shown to be possible, however, attempts to develop an enantioselective variant of the process have so far been unsuccessful.

Acknowledgements

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References

1. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Bergmeire, S. C. *Tetrahedron* **2000**, *56*, 2561; (c) Reetz, M. *Chem. Rev.* **1999**, *99*, 1121; (d) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167; (e) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580; (f) Diguez, M.; Pmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189; (g) Fache, F.; Schulz, E.; Tommasino, L. M.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
2. (a) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911; (b) Mukaiyama, T.; Shiina, U.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708.
3. Examples of direct additions employing O-substituted nucleophiles: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386; (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367; (c) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556; (d) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778; Examples of direct additions employing N-substituted nucleophiles: (e) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2006**, *8*, 2839; (f) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564; (g) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397; (h) Benardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583; (i) Li, L.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 12248.
4. (a) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1543; (b) Willis, M. C.; Piccio, V. J.-D. *Synlett* **2002**, 1625; (c) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.
5. Willis, M. C.; Cutting, G. A.; John, M. P. *Synlett* **2004**, 1195.
6. General procedure for the preparation of acyclic Mannich adducts (Table 1, entry 1): 2,2′-bipyridine (31 mg, 0.2 mmol, 20 mol %), activated powdered 4 Å MS (200 mg) and magnesium perchlorate (44.5 mg, 0.2 mmol, 20 mol %) were stirred for 30 min in THF (2.5 mL) at rt. The suspension formed was then treated with phenyl ketone methyl carbonate (388 mg, 2.0 mmol) in THF (2.5 mL). After 10 min benzaldehyde-derived *N*-tosylimine (259 mg, 1.0 mmol) was added, followed by *N*-methyl morpholine (55 μL, 0.5 mmol). After 24 h the reaction mixture was filtered through Celite, quenched with satd aq solution of NH_4Cl (10 mL) and extracted with EtOAc (2 × 30 mL). The organic layers were washed with satd aq $CuSO_4$ (10 mL), followed by water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, 98:2, DCM/EtOAc) to yield the Mannich adducts as an inseparable mixture of diastereomers (3:1, *anti:syn*) as a white foam (305 mg, 67%); ν_{max}(KBr)/cm^{-1} 3231, 2954–2854, 1761, 1702, 1427, 1186; *anti*-Diastereomer δ_H (300 MHz; $CDCl_3$) 7.76–7.69 (2H, m), 7.62–7.52 (3H, m), 7.47–7.36 (2H, m), 7.18–7.03 (5H, m), 6.98–6.89 (2H, m), 6.11 (1H, d, *J* 3.8), 5.76 (1H, d, *J* 8.3), 5.01 (1H, dd, *J* 8.3, 3.8), 3.75 (3H, s), 2.34 (3H, s, Me); *syn*-Diastereomer δ_H (300 MHz; $CDCl_3$) 7.76–7.69 (2H, m), 7.62–7.52 (3H, m), 7.47–7.36 (2H, m), 7.18–7.03 (5H, m), 6.98–6.89 (2H, m) 5.83 (1H, d, *J* 3.0), 5.55 (1H, d, *J* 8.1), 4.98 (1H, dd, *J* 8.1, 3.0), 3.65 (3H, s), 2.23 (3H, s); δ_C (75 MHz; $CDCl_3$) 192.1, 191.8, 153.6, 153.5, 142.4, 142.1, 136.05, 136.03, 135.9, 133.7, 133.4, 133.0, 132.9, 132.8, 128.5, 128.2, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 126.4, 126.0, 125.96, 125.89, 78.8, 78.3, 56.9, 56.7, 54.5, 54.4, 20.4, 20.0 (2 × Ar signals not observed); *m*/*z* LRMS (EI+) 471.2 ($[M+NH_4]^+$, 100%), 397.2 ($[M+NH_4$, $-CO_2Me$, $-Me]+$, 40%); HRMS (ESI+): $C_{24}H_{27}O_6N_2S$, $[M+NH_4]^+$ requires 471.1590. Found 471.1582.
7. General procedure for the preparation of cyclic Mannich adducts (Table 2, entry 1): 2,2′-bipyridine (21 mg, 0.14 mmol, 20 mol %), activated powdered 4 Å MS (200 mg) and magnesium perchlorate (30 mg, 0.14 mmol, 20 mol %) were stirred for 30 min in THF at rt. The suspension formed was then treated with the phenyl ketone *iso*propenyl carbonate (330 mg, 1.36 mmol, 2 equiv) in THF (2.5 mL). After 10 min benzaldehyde-derived *N*-tosylimine (194 mg, 0.68 mmol, 1 equiv) was added followed by *N*-methyl morpholine (37 μL, 0.34 mmol, 50 mol %). After 48 h the reaction mixture was filtered through Celite and quenched with a satd aq solution of NH_4Cl (10 mL) and extracted with EtOAc (2 × 30 mL). The organic layers were washed with satd aq $CuSO_4$ (10 mL), water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, 98:2, DCM/EtOAc) to yield the cyclic Mannich adducts (203 mg, 71%) as a 20:1 ratio of diastereomers (*cis:trans*); ν_{max}(KBr)/cm^{-1} 2961, 1783, 1702, 1375, 1169; δ_H (400 MHz; $CDCl_3$) 7.56–7.47 (3H, m), 7.39–7.29 (4H, m), 7.14 (1H, t, *J* 7.3), 7.06 (2H, d, *J* 8.3), 6.97 (2H, t, *J* 7.7), 6.78 (2H, d, *J* 7.3), 6.15 (1H, d, *J* 8.4), 5.82 (1H, d, *J* 8.4), 2.35 (3H, s); δ_C (100 MHz; $CDCl_3$) 189.9, 150.7, 145.4, 134.6, 134.4, 134.2, 132.2, 129.3, 129.2, 128.8, 128.5, 128.4, 128.2, 127.7, 79.7, 63.1, 21.6; HRMS (ESI+): $C_{23}H_{19}NNaO_5S$, $[M+Na]^+$ requires 444.0882. Found 444.0886.
8. (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561; (b) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.
9. Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.
10. Iserloh, U.; Oderaotoshi, Y.; Kanemasa, S.; Curran, D. P. *Org. Synth.* **2003**, *80*, 46.