ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 8812

Received 12th July 2013,
Accepted 31st July 2013

DOI: 10.1039/c3cc45278f

www.rsc.org/chemcomm

Catalytic enantioselective Amadori–Heyns rearrangement of racemic α-hydroxy ketones with arylamines: synthesis of optically active α-arylamino ketones†

Angelo Frongia,* Francesco Secci, Francesca Capitta, Pier Paolo Piras and Maria Luisa Sanna

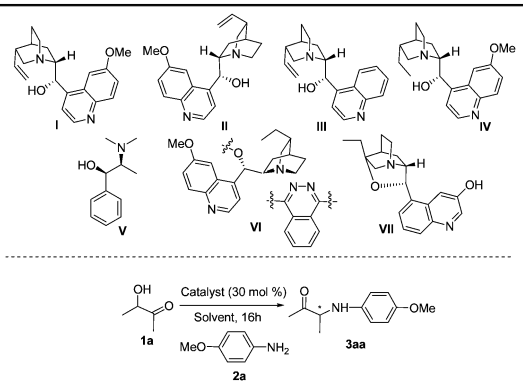
A novel synthesis of optically active α-arylamino ketones through an organocatalytic enantioselective Amadori–Heyns rearrangement is described.

Optically active α-amino ketones are important scaffolds, and have found numerous applications in medicinal chemistry and organic synthesis as building blocks for biologically active compounds and ligands for applications in asymmetric synthesis.[1] An important and widely applied strategy for the construction of these moieties is the catalytic enantioselective ''electrophilic α-amination'' of ketones.[2] However, this approach is often problematic due to the formation of polyaminated side products and, in the case of unsymmetrical ketones, a poor control of the regioselectivity.[3]

As a consequence of the usefulness of α-amino ketones, exploration of a new and atom-economic procedure for the synthesis of these from readily available precursors is still required. The Amadori rearrangement involves the reaction of α-hydroxy-aldehydes (aldoses) with a suitable amine leading to the corresponding 1-amino-1-deoxyketoses (Heyns rearrangement follows the same mechanism but utilizes α-hydroxy-ketones as starting materials).[4] However, to date, despite its great potential for the synthesis of chiral nitrogen-containing carbonyl compounds only a few preparatively useful examples have been reported in the literature (this reaction suffers from a variety of problems such as separation drawbacks, side reactions, further degradation entering into the Maillard reaction cascade *etc.*), and furthermore, an enantioselective version of this reaction has been entirely unknown.

Herein, we report our initial success through the development of an unprecedented case of catalytic enantioselective Amadori–Heyns rearrangement, using cinchona alkaloid catalysts,[5] and its application for the synthesis of optically active α-amino ketones. We initiated the study by investigating the reaction

Table 1 Initial screening studies[a]



Entry	Cat	Ratio of **1a**/**2a** (equiv.)	Solvent	*T*/°C	Yield[b] (%)	ee[c] (%)
1	I	1/1	Toluene	RT	Traces	−6
2	I	3/1	Toluene	RT	20	−42
3	I	5/1	Toluene	RT	20	−40
4	I	10/1	Toluene	RT	78	−40
5	I	10/1	Toluene	0	9	0
6	I	10/1	CH_2Cl_2	RT	62	−24
7	I	10/1	DMF	RT	20	−14
8	I	10/1	THF	RT	28	−34
9	I	10/1	CH_3CN	RT	31	−28
10	I	10/1	MeOH	RT	46	0
11	II	10/1	Toluene	RT	85	25
12	III	10/1	Toluene	RT	79	−32
13	IV	10/1	Toluene	RT	20	−22
14	V	10/1	Toluene	RT	55	18
15	VI	10/1	Toluene	RT	70	0
16	VII[d,e]	10/1	Toluene	RT	95	71

[a] Unless otherwise noted, the reactions were performed with 4.06 mmol of **1a**, 0.406 mmol of **2a**, 0.122 mmol of catalyst, 0.5 mL solvent. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis using a chiral stationary column. Negative values indicate the preferential formation of the opposite enantiomer. [d] The catalyst loading can be reduced to 20 mol% without any detrimental effect on the selectivity (72% ee), although with concomitant decreasing chemical yield (71%). [e] The addition of 4 Å MS as additives led to a slight improvement in the enantioselectivity (73% ee), but with considerable erosion of the yield (62%).

Dipartimento di Scienze Chimiche e Geologiche, Università degli studi di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, I-09042, Monserrato, Cagliari, Italy. E-mail: afrongia@unica.it; Fax: +39 0706754388; Tel: +39 0706754405

† Electronic supplementary information (ESI) available: Experimental protocols, proof of the absolute stereochemical configuration, copies of NMR spectra and HPLC chromatograms. See DOI: 10.1039/c3cc45278f

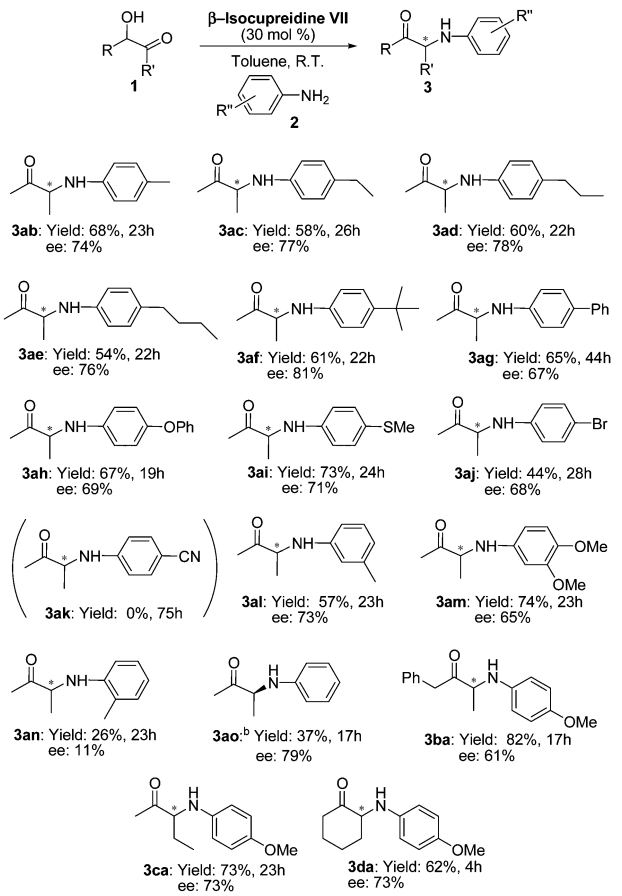
of acetoin **1a** with *p*-anisidine **2a**, using 30 mol% of quinidine **I** as catalyst. As shown in Table 1 the reactions generally proceed with moderate enantiocontrol, but both the yield and enantioselectivity were strongly influenced by the variation in the reaction conditions, including the molar ratios of **1a** and **2a**, temperatures, as well as solvents (entries 1–10).

The subsequent optimization of our protocol has been carried out by screening the catalytic performance of different chiral tertiary amines **II-VII** (entries 11–16). Gratifyingly, the use of β-isocupreidine **VII** in toluene was entirely satisfactory: an excellent chemical yield (95%) was combined with a good enantioselectivity of 71% ee (entry 16).

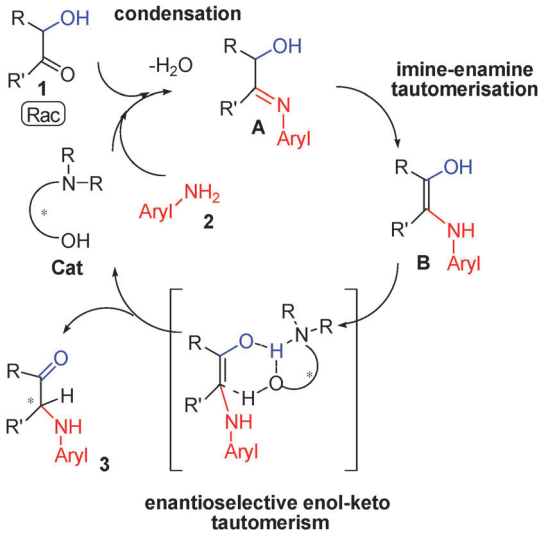
With the optimized conditions in hand, the substrate scope was investigated and the results are summarized in Table 2. There appears to be significant tolerance to structural and electronic variations of anilines **2**, to enable access to a broad variety of densely functionalized α-arylamino ketone derivatives **3**.

In general, the best results were obtained using *para*-substituted anilines giving rise to both good to high yields and good enantioselectivities of up to 81% ee (**3ab–3ai**) except for the bromine-substituted aniline **2j** (44% yield; 68% ee).

Table 2 Preliminary scope of the reaction[a]



[a] Conditions: 4.06 mmol of **1**, 0.406 mmol of **2**, 0.122 mmol of β-isocupreidine, 0.5 mL toluene at room temperature. Yields are the isolated yields after flash chromatography. Enantiopurity of the products was determined by HPLC analysis using a chiral stationary column. [b] For proof of the absolute stereochemical configuration, see the ESI.



Scheme 1 Proposed catalytic cycle.

On the other hand, a representative aniline bearing a strongly electron-withdrawing group such as *para*-CN in **2k** failed to participate in this reaction which we attribute to its lower basicity. *meta*-Substituted anilines, such as **2l** and **2m**, performed almost equally well in this reaction (57–74% yield; 65–73% ee) whereas *ortho*-substituted anilines, such as **2n**, furnished the desired product **3an** in 26% yield with only 11% ee, presumably for steric reasons.

Gratifyingly, unsubstituted aniline **2o** gave the corresponding amination product **3ao** with good enantioselectivity (79% ee), although, with low chemical yield (37%).

Under the optimized reaction conditions, the Amadori–Heyns rearrangement of 3-hydroxy-4-phenylbutan-2-one **1b** and 2-hydroxypentan-3-one **1c**, using **2a** as a representative aniline, has also been examined. It was found that for 3-hydroxy-4-phenylbutan-2-one **1b**, the corresponding α-amino ketone **3ba** was obtained in high yield (82%) with 61% ee and for 2-hydroxypentan-3-one **1c**, the corresponding α-amino ketone **3ca** was obtained in 73% yield with good ee (73%), respectively. Meanwhile, we found that a cyclic α-hydroxy ketone such as 2-hydroxycyclohexanone **1d** was tolerated under the reaction conditions and provided the desired product **3da** in good yield (62%) with good enantioselectivity (73% ee).

The reaction can be rationalized by assuming the mechanism shown in Scheme 1. The cinchona alkaloid β-isocupreidine catalyzes the generation of 1,2-enaminol **B** from **1** and **2** followed by an *in situ* enantioselective enol–keto tautomerisation.[6] In view of the related protonation protocols[7] an analogous stereochemical model can be formulated: the hydrogen bonding between the enaminol proton and the tertiary nitrogen of the catalyst enhances the electron density at α-C and leads to more or less concerted proton transfer, *via* a cyclic, six-membered ring transition state.[8]

In conclusion, we have developed the first enantioselective catalytic Amadori–Heyns rearrangement for the synthesis of α-arylamino ketones. The products have been isolated in good to high yields and up to 81% ee. The optimisation and extension of this reaction, as well as studies aimed at increasing the enantioselectivity are currently under investigation in our laboratories.

Financial support from the MIUR, Rome, and from the University of Cagliari (National Project ''Stereoselezione in Sintesi Organica Metodologie ed Applicazioni'') and from CINMPIS and FIRB 2008 is gratefully acknowledged.

Notes and references

1 (*a*) J. P. Genet, C. Greck and D. Lavergne, in *Modern Amination Methods*, ed. A. Ricci, Wiley-VCH, New York, 2000, p. 65; (*b*) S. Baktharaman, R. Hili and A. K. Yudin, *Aldrichimica Acta*, 2008, **41**, 109–118; (*c*) F. Colpaert, S. Mangelinckx, B. Denolf and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 6023–6032, and references cited therein.

2 (*a*) R. O. Duthaler, *Angew. Chem., Int. Ed.*, 2003, **42**, 975–978; (*b*) E. Erdik, *Tetrahedron*, 2004, **60**, 8747–8782; (*c*) C. Greck, B. Drouillat and C. Thomassigny, *Eur. J. Org. Chem.*, 2004, 1377–1385; (*d*) T. Vilaivan and W. Bhanthumnavin, *Molecules*, 2010, **15**, 917–958; (*e*) A. M. R. Smith and K. K. (Mimi) Hii, *Chem. Rev.*, 2011, **111**, 1637–1656.

3 (*a*) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 6254–6255; (*b*) G. Dessole, L. Bernardi, B. F. Bonini, E. Capitò, M. Fochi, R. P. Herrera, A. Ricci and G. Cahiez, *J. Org. Chem.*, 2004, **69**, 8525–8528; (*c*) P. Kotrusz, S. Alemayehu, S. Toma, H.-G. Schmalz and A. Adler, *Eur. J. Org. Chem.*, 2005, 4904–4911.

4 The Amadori–Heyns rearrangement is very well known in carbohydrate and food chemistry, see: (*a*) L. C. Maillard, *C. R. Seances Acad. Sci., Ser. 2*, 1912, **154**, 66–68; (*b*) M. Amadori, *Atti. R. Accad. Naz. Lincei*, 1931, **13**(6), 72; (*c*) R. Kuhn and F. Weygand, *Chem. Ber.*, 1937, **70**, 769; (*d*) K. Heyns and W. Koch, *Z. Naturforsch., B*, 1952, **7**, 486–488; (*e*) H. S. Isbell and H. L. Frush, *J. Org. Chem.*, 1958, **23**, 1309–1319; (*f*) J. Yoshimura and M. Funabashi, *Carbohydr. Res.*, 1969, **11**, 276–281; (*g*) D. Xenakis, N. Moll and B. Gross, *Synthesis*, 1983, 541–543; (*h*) F. Ledl and E. Schleicher, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 565–594; (*i*) S. N. Noomen, G. J. Breel and C. Winkel, *Recl. Trav. Chim. Pays-Bas*, 1995, **114**, 321–324; (*j*) T. J. Guzi and T. L. Macdonald, *Tetrahedron Lett.*, 1996, **37**, 2939–2942; (*k*) T. M. Wrodnigg and B. Eder, in *Glycoscience-Epimerization Isomerization Rearrangement Reactions of Carbohydrates*, ed. A. E. Stütz, Springer, 2001, pp. 115–152; (*l*) R. J. Ferrier, *Carbohydrates Chemistry*, 2002, vol. 33, pp. 126–143; (*m*) L. A. Paquette and J. E. Hofferberth, *Org. React.*, 2004, 477–567; (*n*) K. Maruoka and H. Yamamoto, *Comp. Org. Synth.*, 1991, **6**, 789–791; (*o*) T. M. Wrodnigg, C. Kartusch and C. Illaszewicz, *Carbohydr. Res.*, 2008, **343**, 2057–2066; (*p*) K. Gallas, G. Pototschnig, F. Adanitsch, A. E. Stütz and T. M. Wrodnigg, *Beilstein J. Org. Chem.*, 2012, **8**, 1619–1629; (*q*) T. M. Wrodnigg and A. E. Stütz, *Angew. Chem., Int. Ed.*, 1999, **38**, 827–828; (*r*) Y. Shan, F. Oulaidi and M. Lahmann, *Tetrahedron Lett.*, 2013, **54**, 3960–3961.

5 For reviews on cinchona alkaloid catalysts, see: (*a*) C. E. Song, *Cinchona Alkaloids in Synthesis & Catalysis*, Wiley-VCH, Weinheim, 2009; (*b*) S. J. Connon, *Chem. Commun.*, 2008, 2499–2510; (*c*) T. Marcelli and H. Hiemstra, *Synthesis*, 2010, 1229–1279; (*d*) E. M. O. Yeboah, S. O. Yeboah and G. S. Singh, *Tetrahedron*, 2011, **67**, 1725–1762.

6 For a tandem imine–enamine/keto–enol tautomerization of transient α-hydroxy imines, see: (*a*) T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194–196. For similar transformations, see: (*b*) N. De Kimpe, L. Mones, R. Verhe, L. De Buyck and N. Schamp, *Tetrahedron Lett.*, 1982, **23**, 789–792; (*c*) N. De Kimpe, L. D'Hondt and L. Mones, *Tetrahedron*, 1992, **48**, 3183–3208; (*d*) A. Adams and N. De Kimpe, *Chem. Rev.*, 2006, **106**, 2299–2319; (*e*) F. Van Lancker, A. Adams and N. De Kimpe, *J. Agric. Food Chem.*, 2012, **60**, 4697–4708. For seminal studies on tandem processes involving enantioselective organocatalytic enol–keto tautomerisation, see: (*f*) E. Schmitt, I. Schiffers and C. Bolm, *Tetrahedron Lett.*, 2009, **50**, 3185–3188.

7 For reviews on enantioselective protonation, see: (*a*) A. Claraz, S. Oudeyer and V. Levacher, *Curr. Org. Chem.*, 2012, **16**, 2191–2205; (*b*) J. T. Mohr, A. Y. Hong and B. M. Stoltz, *Nat. Chem.*, 2009, **1**, 359–369; (*c*) L. Duhamel, P. Duhamel and J. C. Plaquevent, *Tetrahedron: Asymmetry*, 2004, **15**, 3653–3691; (*d*) C. Fehr, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2566–2587. For examples of organocatalytic enantioselective protonation, see: (*e*) O. Piva, R. Mortezaei, F. Henin, J. Muzart and J. P. Pete, *J. Am. Chem. Soc.*, 1990, **112**, 9263–9272; (*f*) C. Schaefer and G. C. Fu, *Angew. Chem., Int. Ed.*, 2005, **44**, 4606–4608; (*g*) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer and V. Levacher, *Angew. Chem., Int. Ed.*, 2007, **46**, 7090–7092; (*h*) C. H. Cheon and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 9246–9247; (*i*) B. Wang, F. Wu, Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 768–769; (*j*) M. Rueping, W. Ieawsuwan, A. P. Antonchick and B. J. Nachtsheim, *Angew. Chem., Int. Ed.*, 2007, **46**, 2097–2100; (*k*) M. Rueping and W. Ieawsuwan, *Adv. Synth. Catal.*, 2009, **351**, 78–84; (*l*) H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 2860–2861; (*m*) N. Fu, L. Zhang, J. Li, S. Luo and J.-P. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 11451–11455; (*n*) T. Jousseaume, N. E. Wurz and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1410–1414. For a catalytic enantioselective tandem protonation-semipinacol rearrangement of 2-oxo allylic alcohols, see: (*o*) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao and P. Gu, *Angew. Chem., Int. Ed.*, 2009, **48**, 8572–8574. For a catalytic enantioselective ketimine tautomerization to the corresponding aldimine in the course of biomimetic transamination, see: (*p*) X. Xiao, Y. Xie, C. Su, M. Liu and Y. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 12914–12917. For personal research accounts, see: (*q*) F. Capitta, A. Frongia, P. P. Piras, P. Pitzanti and F. Secci, *Adv. Synth. Catal.*, 2010, **352**, 2955–2960; (*r*) F. Capitta, A. Frongia, P. P. Piras, P. Pitzanti and F. Secci, *Org. Biomol. Chem.*, 2012, **10**, 490–494.

8 In order to clarify the mechanism of the chiral induction a control experiment was performed according to a reviewer's comment. Mixing the optically active **3aa** (71% ee) under optimum reaction conditions (30 mol% of β-isocupreidine in toluene at room temperature) after 7 h showed a slight loss of ee (69%), suggesting that the kinetic control is probably responsible for the observed results. We thank the reviewer for his valuable suggestion.

