ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3094–3096

www.rsc.org/chemcomm

COMMUNICATION

Tuning the reactivity of Au-complexes in an Au(I)/chiral Brønsted acid cooperative catalytic system: an approach to optically active fused 1,2-dihydroisoquinolines†

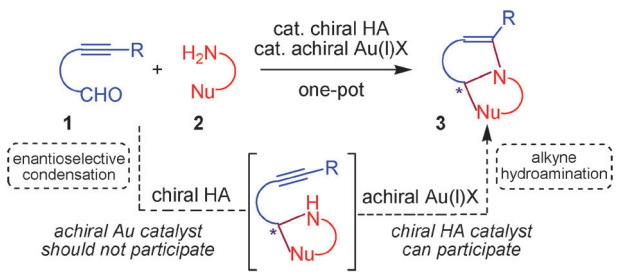
Nitin T. Patil,* Anil Kumar Mutyala, Ashok Konala and Ramesh Babu Tella

Received 29th November 2011, Accepted 27th January 2012
DOI: 10.1039/c2cc17450b

An enantioselective cooperative catalysis protocol, utilizing achiral Au(I) complexes and chiral Brønsted acids, has been developed for the synthesis of optically pure fused 1,2-dihydroisoquinolines starting from 2-alkynylbenzaldehydes and 2-aminobenzamides.

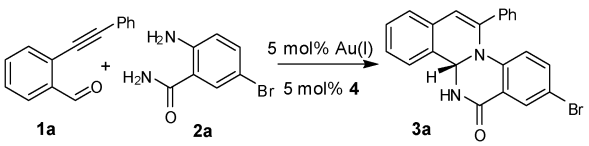
The enantioselective cooperative/relay catalysis combining metal catalysis and organocatalysis has emerged as a promising strategy in organic synthesis.[1] The concept is extremely challenging because practically it is difficult to discover the right choice of chiral metal catalyst and/or organocatalyst combination. Unlike biological processes in which Nature takes advantage of enzyme architecture to facilitate a reaction cascade, it is difficult to conduct such reactions in a flask because of the compatibility issues with the starting materials, intermediates and other catalysts present from the onset of the reaction. Often tuning of reactivity of either of the catalysts is necessary in order to make the catalytic system compatible. In particular, a cooperative process wherein soft transition metal ions are employed to activate alkyne functionality[2] would be considered a difficult task. While in the literature some reports describe this chemistry,[3] there exist only few examples of an enantioselective process that utilizes achiral Au catalysts and chiral Brønsted acids as catalysts.[4]

Fused 1,2-dihydroisoquinolines are of broad interest due to their vast abundance in natural products[5] and pharmaceutically important compounds.[6] Noteworthily, to the best of our knowledge, no convergent enantioselective methods leading to the formation of optically active 1,2-dihydroisoquinolines have been disclosed in the literature so far.[7] Given the importance of these fused isoquinoline derivatives and their potential biological properties, the development of new methodologies for their preparation in an enantioselective manner is of great importance for organic and medicinal chemists.



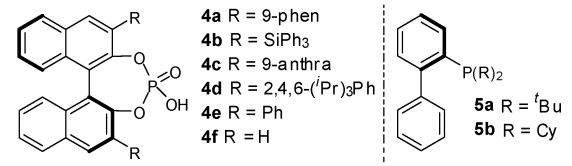
Scheme 1

Table 1 Feasibility and optimization studies[a]



Entry	Au	HA (**4**)	Solvent	Yield[b] (%)	er[c]
1	AuCl	**4a**	DCE	90	50 : 50
2	Ph_3PAuCl	**4a**	DCE	41	61 : 39
3	$Ph_3PAuOTf$	**4a**	DCE	82	69 : 31
4	$Ph_3PAuSbF_6$	**4a**	DCE	49	74 : 26
5	Ph_3PAuBF_4	**4a**	DCE	46	59 : 41
6	Ph_3PAuMe	**4a**	DCE	72	89 : 11
7	**5a**–AuMe	**4a**	DCE	63	84 : 16
8	**5b**–AuMe	**4a**	DCE	61	85 : 15
9	Ph_3PAuMe	**4b**	DCE	05[d]	89 : 11
10	Ph_3PAuMe	**4c**	DCE	92	92 : 08
11	Ph_3PAuMe	**4d**	DCE	83	39 : 61[e]
12	Ph_3PAuMe	**4e**	DCE	82	69 : 31
13	Ph_3PAuMe	**4f**	DCE	91	56 : 44
14	**Ph_3PAuMe**	**4c**	**DCE**	**92**	**98 : 02**[f,g]
15	Ph_3PAuMe	**4c**	CH_3CN	74	96 : 04[f]
16	Ph_3PAuMe	**4c**	THF	57	82 : 18[f]
17	Ph_3PAuMe	**4c**	Toluene	65	90 : 10[f]
18	Ph_3PAuMe	**4c**	$CHCl_3$	92	92 : 08[f]

[a] Reaction conditions: 0.24 mmol **1a**, 0.24 mmol **2a**, 5 mol% **4**, 5 mol% Au catalysts, 50 mg MS 4 Å, solvent (2 mL), 0 °C, 24 h then rt, 24 h. [b] Isolated yields. [c] From HPLC analysis using an OD-H column. [d] Recovery of corresponding aminal (91 : 09 er) in 85% yield. [e] Opposite enantiomer was obtained. [f] 2 mol% PPh_3AuMe. [g] −5 °C, 32 h then rt, 24 h.



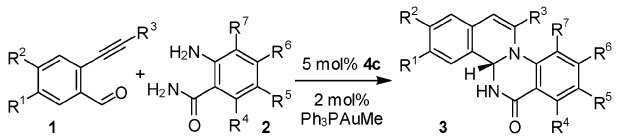
CPC Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India. E-mail: nitin@iict.res.in; Fax: +91-40-27193382

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc17450b

A central theme of the research in our laboratory is the development of π-acid catalyzed reactions[8] and merging π-acid catalysis with organocatalysis[9] for the synthesis of nitrogen containing heterocycles. Recently, we reported an AuCl-catalyzed coupling–cyclization strategy for the synthesis of isoquinoline-fused polycyclic compounds employing 2-alkynylbenzaldehydes and various aromatic amines bearing tethered nucleophiles.[8b] On the basis of the proposed rudimentary mechanism, we postulated that the reaction can be made enantioselective under a cooperative catalysis utilizing achiral Au(I) complexes and chiral Brønsted acids[10] to give optically active heterocycles as outlined in Scheme 1. A major concern is that the Au(I)X salts would racemize the relatively labile optically pure aminals, generated *in situ* by the enantioselective condensation of **1** with **2**, leading to the racemic products **3**. The challenge, therefore, was to search for a suitable achiral gold(I) catalyst which should only catalyze hydroamination and should not take part in the condensation process. We surmised that this crucial tuning of Lewis acidity of gold(I) complexes can be achieved by varying the counter-ion.[11]

To test this newly proposed idea of cooperative catalysis, we began by choosing readily available 2-phenylalkynylbenzaldehyde (**1a**) and 2-amino-5-bromobenzamide (**2a**)[12] as the coupling partners using a catalyst combination of Au(I) salts and chiral phosphoric acids. The results of this study are summarized in Table 1. At the outset, the proposed enantioselective reaction was performed using **1a**, **2a**, 5 mol% AuCl and 5 mol% of **4a** in DCE at 0 °C, 24 h then at rt for 24 h (entry 1). The desired product **3a** was obtained in 90% yield; however, the er was found to be 50 : 50. The use of 5 mol% Ph_3PAuCl and 5 mol% of **4a** afforded **3a** in 41% yield and 61 : 39 er (entry 2). Under the similar reaction conditions, various cationic Au complexes such as $Ph_3PAuOTf$ (entry 3), $Ph_3PAuSbF_6$ (entry 4) and Ph_3PAuBF_4 (entry 5) were examined. None of the above reactions showed higher enantioselectivity of the product, but validated our proposal that the tuning of counter-ion might have a significant role in obtaining the product with higher enantioselectivity. Consequently, the enantioselective condensation/hydroamination cascade was attempted using Ph_3PAuMe and **4a**. Gratifyingly, the reaction gave the product **3a** in 72% yield in 89 : 11 enantiomeric ratio (entry 6). In order to know the effect of the phosphine ligand, the Au complexes **5a** and **5b** were synthesized and tested for their reactivities (entries 7 and 8). In both the cases, the reaction was found to be very sluggish indicating that the sterically bulky phosphine ligands hamper the rate of hydroamination reaction. Next, our studies were aimed at the screening of chiral phosphoric acid catalysts **4** bearing various type of substituents at the 3,3′-position on the binaphthyl backbone. As shown in entries 9–13, all of the chiral catalysts **4** exhibited excellent performance in terms of yields (except entry 9); however, enantioselectivities were found to be strongly dependent on the C-3 substituents. Out of the chiral phosphoric acids examined, the catalyst **4c** was proved to be the best, giving

Table 2 Substrate scope for the enantioselective synthesis of fused 1,2-dihydroisoquinolines **3**[a,b]



Entry	1	2	3	Yield (%)	er
1	**1a** R^1, R^2 = H, R^3 = Ph	**2b** R^4, R^5, R^6, R^7 = H	**3b**[c]	82	94 : 06
2	**1a**	**2c** R^4 = F, R^5, R^6, R^7 = H	**3c**	76	90 : 10
3	**1a**	**2d** R^4 = Cl, R^5, R^6, R^7 = H	**3d**[d]	59	81 : 19
4	**1a**	**2e** R^4, R^5, R^7 = H, R^6 = Cl	**3e**[d]	64	97 : 03
5	**1a**	**2f** R^4, R^6, R^7 = H, R^5 = OMe	**3f**[d]	71	95 : 05
6	**1a**	**2g** R^5, R^6, R^7 = H, R^4 = Me	**3g**[d]	65	93 : 07
7	**1a**	**2h** R^4, R^6 = H, R^5 = Cl, R^7 = Me	**3h**[d,e]	36	81 : 19
8	**1b** R^1 = H, R^2 = Me, R^3 = Ph	**2b**	**3i**	74	90 : 10
9	**1c** R^1 = F, R^2 = H, R^3 = Ph	**2b**	**3j**	86	99 : 01
10	**1c**	**2a**	**3k**	89	99 : 01
11	**1d** R^1, R^2 = H, R^3 = *p*-tolyl	**2a**	**3l**	93	98 : 02
12	**1d**	**2b**	**3m**	84	97 : 03
13	**1e** R^1 = F, R^2 = H, R^3 = *p*-tolyl	**2b**	**3n**	93	99 : 01
14	**1e**	**2a**	**3o**	95	97 : 03
15	**1f** R^1, R^2 = H, R^3 = *p*-^{t}but-phenyl	**2b**	**3p**	86	93 : 07
16	**1f**	**2a**	**3q**	91	97 : 03
17	**1f**	**2f**	**3r**	81	90 : 10
18	**1f**	**2c**	**3s**	91	98 : 02
19	**1g** R^1, R^2 = H, R^3 = *m*-OMe–Ph	**2b**	**3t**	78	94 : 06
20	**1h** R^1, R^2 = H, R^3 = 3,5-di-methylphenyl	**2b**	**3u**	91	95 : 05
21	**1h**	**2a**	**3v**	92	98 : 02
22	**1i** R^1, R^2 = H, R^3 = 1-cyclohexenyl	**2b**	**3w**	84	94 : 06
23	**1i**	**2a**	**3x**	90	97 : 03
24	**1j** R^1, R^2 = H, R^3 = cyclohexyl	**2a**	**3y**[c]	84	98 : 02

[a] Reaction conditions: 0.24 mmol **1**, 0.24 mmol **2**, 5 mol% **4c**, 2 mol% Ph_3PAuMe, 50 mg MS 4 Å, DCE (2 mL), −5 °C, 32 h, then rt 24 h. [b] Isolated yields. [c] −5 °C, 32 h then rt 48 h. [d] 5 mol% **4c**, 5 mol% Ph_3PAuMe, −5 °C, 32 h then rt 48 h. [e] Corresponding aminal obtained in 52% yield with 84 : 16 er.

3a in 92% yield and 92 : 08 er (entry 10). Interestingly, lowering the catalyst loading of PPh_3AuMe resulted in a slight increase in enantiomeric ratio, 98 : 02 (entry 14). As can be judged from entries 15–18, solvents such as CH_3CN, THF, toluene and $CHCl_3$ are not superior.

Next, the reaction of 2-alkynylbenzaldehydes **1** with various 2-aminobenzamides **2** was examined under the optimized conditions (Table 1, entry 14) and the representative results are summarized in Table 2. The reaction proved to be general, since 2-aminobenzamides, bearing substituents at various positions in the aromatic ring, reacted effectively with various 2-alkynylbenzaldehydes to afford the target products in moderate to good overall yields (59–95%) and excellent enantioselectivities (81 : 19–99 : 01 er). However, in the case of **3h** the reaction was found to be sluggish. In some of the cases the amount of Au catalysts used had to be re-optimized, in order to avoid unreacted aminals in the crude reaction mixtures or to increase the formation of **3d**, **3e**, **3f**, **3g** and **3h**. It is worth noting that the halo substituent on the 2-aminobenzamides had no significant influence on the reactivity. The halo-substituted fused isoquinolines can serve as versatile synthons[13] enabling introduction of various functional groups. Importantly, the reaction conditions are so mild that no significant dehydrogenation took place even after stirring for a long time and the final products **3a–y** were obtained in high enantiomeric ratios.[13]

In summary, we developed an enantioselective cooperative catalytic protocol in which tuning the reactivity of the Au(I) center is a crucial factor for obtaining the product with high ee's.

NTP and AKM/AK thanks DST and CSIR for financial assistance.

Notes and references

1 Reviews: (*a*) N. T. Patil, V. S. Shinde and B. Gajula, *Org. Biomol. Chem.*, 2012, **10**, 211–224; (*b*) N. T. Patil, *Angew. Chem., Int. Ed.*, 2011, **50**, 1759–1761; (*c*) S. Piovesana, D. M. S. Schietroma and M. Bella, *Angew. Chem., Int. Ed.*, 2011, **50**, 6216–6232; (*d*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422–434; (*e*) C. Zhong and X. Shi, *Eur. J. Org. Chem.*, 2010, 2999–3025; (*f*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745–2755.

2 Selected recent reviews on π-activation: (*a*) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657–1712; (*b*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442; (*c*) S. F. Kirsch, *Synthesis*, 2008, 3183–3204; (*d*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351–3378; (*e*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239–3265; (*f*) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266–3325; (*g*) N. Bongers and N. Krause, *Angew. Chem., Int. Ed.*, 2008, **47**, 2178–2181; (*h*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410–3449; (*i*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211.

3 Reviews: (*a*) A. S. K. Hashmi and C. Hubbert, *Angew. Chem., Int. Ed.*, 2010, **49**, 1010–1012; (*b*) A. Duschek and S. F. Kirsch, *Angew. Chem., Int. Ed.*, 2008, **47**, 5703–5705. For other examples, see: (*c*) B. Montaignac, M. R. Vitale, V. Ratovelomanana-Vidal and V. Michelet, *Eur. J. Org. Chem.*, 2011, 3723–3727; (*d*) J. T. Binder, B. Crone, T. T. Haug, H. Menz and S. F. Kirsch, *Org. Lett.*, 2008, **10**, 1025–1028; (*e*) T. Yang, A. Ferrali, L. Campbell and D. J. Dixon, *Chem. Commun.*, 2008, 2923–2925; (*f*) K. L. Jensen, P. T. Franke, C. Arróniz, S. Kobbelgaard and K. A. Jørgensen, *Chem.–Eur. J.*, 2010, **16**, 1750–1753; (*g*) S. Belot, K. A. Vogt, C. Besnard, N. Krause and A. Alexakis, *Angew. Chem., Int. Ed.*, 2009, **48**, 8923–8926; (*h*) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959–4962.

4 (*a*) M. Kojima and K. Mikami, *Synlett*, 2012, 57–61; (*b*) C. Wang, Z.-Y. Han, H.-W. Luo and L.-Z. Gong, *Org. Lett.*, 2010, **12**, 2266–2269; (*c*) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner and F. D. Toste, *Angew. Chem., Int. Ed.*, 2010, **49**, 598–601; (*d*) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182–9183; (*e*) K. Aikawa, M. Kojima and K. Mikami, *Angew. Chem., Int. Ed.*, 2009, **48**, 6073–6077; (*f*) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science*, 2007, **317**, 496–499; (*g*) X.-Y. Liu and C.-M. Che, *Org. Lett.*, 2009, **11**, 4204–4207.

5 Selected recent reviews: (*a*) K. W. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 444–463; (*b*) K. W. Bentley, *Nat. Prod. Rep.*, 2005, **22**, 249–268; (*c*) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341–3370.

6 Selected references: (*a*) L. V. Smith, A. D. C. Parenty, K. M. Guthrie, J. Plumb, R. Brown and L. Cronin, *ChemBioChem*, 2006, **7**, 1757–1763; (*b*) R. J. Griffin, G. Fontana, B. T. Golding, S. Guiard, I. R. Hardcastle, J. J. J. Leahy, N. Martin, C. Richardson, L. Rigoreau, M. Stockley and G. C. M. Smith, *J. Med. Chem.*, 2005, **48**, 569–585; (*c*) A. D. C. Parenty, L. V. Smith, K. M. Guthrie, D.-L. Long, J. Plumb, R. Brown and L. Cronin, *J. Med. Chem.*, 2005, **48**, 4504–4506; (*d*) D. Scholz, H. Schmidt, E. E. Prieschl, R. Csonga, W. Scheirer, V. Weber, A. Lembachner, G. Seidl, G. Werner, P. Mayer and T. Baumruker, *J. Med. Chem.*, 1998, **41**, 1050–1059; (*e*) W. J. Houlihan, P. G. Munder, D. A. Handley, S. H. Cheon and V. A. Parrino, *J. Med. Chem.*, 1995, **38**, 234–240.

7 (*a*) S. Obika, H. Kono, Y. Yasui, R. Yanada and Y. Takemoto, *J. Org. Chem.*, 2007, **72**, 4462–4468; (*b*) R. Yanada, S. Obika, H. Kono and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2006, **45**, 3822–3825; (*c*) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959–4962; (*d*) N. Asao, Y. S. Salprima, T. Nogami and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 5526–5528.

8 (*a*) N. T. Patil and V. Singh, *J. Organomet. Chem.*, 2011, **696**, 419–432; (*b*) N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, P. V. K. Raju and B. Sridhar, *Eur. J. Org. Chem.*, 2010, 1999–2007.

9 (*a*) N. T. Patil and V. S. Raut, *J. Org. Chem.*, 2010, **75**, 6961–6964; (*b*) N. T. Patil and A. Konala, *Eur. J. Org. Chem.*, 2010, 6831–6839.

10 For reviews on enantioselective Brønsted acid catalysis, see: (*a*) A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (*c*) M. Terada, *Chem. Commun.*, 2008, 4097–4112; (*d*) M. Terada, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 101–119; (*e*) D. Kampen, C. M. Reisinger and B. List, *Top. Curr. Chem.*, 2009, **291**, 395–456.

11 R. L. LaLonde, B. D. Sherry, E. J. Kang and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 2452–2453.

12 (*a*) M. Rueping, A. P. Antonchick, E. Sugiono and K. Grenader, *Angew. Chem., Int. Ed.*, 2009, **48**, 908–910; (*b*) X. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 15786–15787.

13 See ESI† for mechanistic studies, diversification of products and related information.

