Tetrahedron Letters 54 (2013) 5865–5868

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of benzannulated spiroacetals using chiral gold–phosphine complexes and chiral anions

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ARTICLE INFO

Article history:
Received 16 June 2013
Revised 26 July 2013
Accepted 21 August 2013
Available online 31 August 2013

Keywords:
Gold catalysis
Spiroacetals
Asymmetric synthesis
Chiral catalysts

ABSTRACT

The development of an asymmetric gold-catalysed dihydroalkoxylation strategy for the synthesis of the 3′*H*-spiro[chroman-2,1′-isobenzofuran] spiroacetal ring system **5** is described. Spiroacetal was generated in up to 87:13 enantiomeric ratio using chiral gold–phosphine complexes and chiral silver phosphate Ag(*S*)-TRIP.

The 5,6-benzannulated spiroacetal moiety is a key pharmacophore found in a variety of natural products exhibiting interesting biological activity, such as paecilospirone,[1] berkelic acid[2] and the rubromycins[3] (Fig. 1). In particular, paecilospirone, an antimitotic agent isolated from the marine fungus *Paecilomyces* sp.,[1] was recently synthesised by our group.[4] To date, there has been limited work on the construction of the paecilospirone spiroacetal ring system[5] and the development of methods for the reagent-controlled asymmetric catalytic synthesis of spiroacetals has only recently emerged.

Gold catalysis has developed into a robust synthetic tool for the addition of heteroatoms to carbon–carbon multiple bonds under mild conditions.[6] Whilst spiroacetals have been assembled using gold catalysis,[7] extension of this valuable synthetic method to the enantioselective synthesis of spiroacetals has only recently been reported. Ding and coworkers developed an Ir(I)/SpinPHOX-catalysed asymmetric hydrogenation and spirocyclisation of α,α′-bis(2-hydroxyarylidene) ketones for the formation of enantio-enriched spiroacetals.[8] List and Nagorny have independently reported the chiral phosphoric acid catalysed enantioselective spiroacetalisation of enol ethers.[9,10] In addition, Gong and coworkers reported a gold(I)/Bronsted acid relay catalytic three-component cascade reaction to generate highly enantioenriched spiroacetals.[11] During the preparation of this manuscript, Hashmi et al. also reported highly active NAC-gold catalysts for the synthesis of phenols and spiroacetals.[12] Our ongoing interest in the synthesis of benzannulated spiroacetals[4,5,13] prompted us to investigate the use of chiral gold-ligand complexes to catalyse the enantioselective spirocyclisation of dihydroxyalkyne **2** to construct the spiroacetal ring system **1** of paecilospirone. Herein we report an asymmetric gold-catalysed dihydroalkoxylation strategy for the synthesis of the 3′*H*-spiro[chroman-2,1′-isobenzofuran] ring system **5**.

We envisaged that the spiroacetal would be generated via metal-catalysed spirocyclisation of dihydroxyalkyne **2**, accessible from Sonogashira coupling of **3** and **4**. Iodide **3** and alkyne **4** in turn would be prepared easily from commercially available reagents (Scheme 1). The cyclisation precursor, dihydroxyalkyne **2** was prepared by Sonogashira coupling of iodide **3**[14] with alkyne **4**[14] using $Pd(OAc)_2$ and 1,1′-bis(di-*tert*-butylphosphino)ferrocene (dtbpf) followed by cleavage of both protecting groups with 20 mol % *p*-toluenesulfonic acid (Scheme 2).

With dihydroxyalkyne **2** in hand, we focused our attention on the gold-catalysed enantioselective spirocyclisation to form spiroacetal **1** (Table 1). Initially, various metal catalysts (Pd, Cu and Au) were screened for their ability to effect the dihydroalkoxylation of **2**.

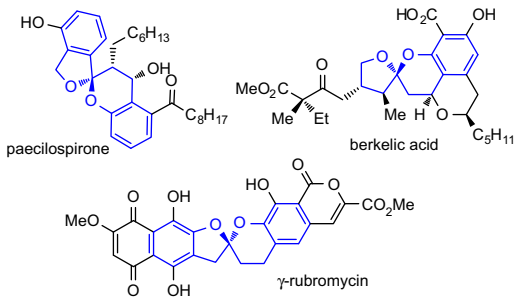

Figure 1. Structures of 5,6-benzannulated spiroacetal natural products: paecilospirone, berkelic acid and γ-rubromycin.

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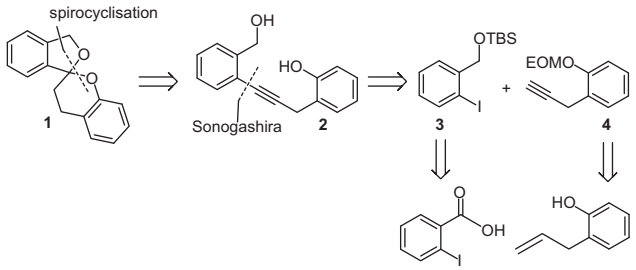
http://dx.doi.org/10.1016/j.tetlet.2013.08.077

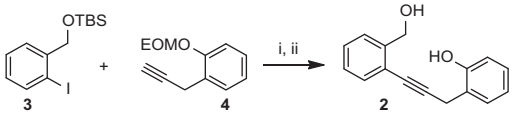


Scheme 1. Retrosynthetic strategy.

A regioisomeric mixture of spiroacetals **1** and **5** resulted with all the catalytic systems.[15] Products **1** and **5** were separable by chromatography, however, the composition of mixtures could be determined by ^{1}H NMR. The catalyst screen revealed that $AuPPh_3Cl$ in the presence of $AgSbF_6$ in dichloromethane was initially the most effective for the spirocyclisation of **2** (entry 7). Good selectivity for **1** was obtained with the inclusion of the racemic biaryl phosphine ligand, BINAP (**6**) (entry 8). Surprisingly, a change in selectivity in favour of **5** was observed following a change in solvent from dichloromethane to 1,4-dioxane (entry 9) that was even more pronounced upon changing from $AuPPh_3Cl$ to $AuCl_3$ (entry 10) indicating that both the nature of the gold catalyst and the solvent influenced the regioselectivity of the spirocyclisation. $AuCl{\cdot}SMe_2$ gave similar selectivity and yields to $AuPPh_3Cl$ and was therefore used in subsequent experiments (entries 15 and 16).

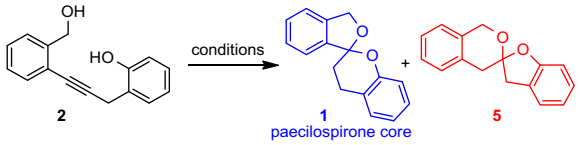
With the optimised conditions in hand (entry 8), a range of chiral ligands were next investigated for their ability to influence the chirality established in the spirocyclisation reaction (Fig. 2). The use of chiral phosphine ligands (*S*)-BINAP (**6**) and (*R*)-MeO-BIPHEP (**7**) resulted in a complete lack of asymmetric induction with only racemic material obtained (entries 11 and 12). Disappointingly, lowering the reaction temperature to −40 °C resulted in no reaction (entry 13), but at this temperature the (*R*)-MeO-BIPHEP (**7**) ligand showed good reactivity and an increase in selectivity for spiroacetal **1** (entry 14). This result suggests that the formation of spiroacetal **1** may be kinetically favoured. Alternative chiral ligands such as (*R*,*S*)-Josiphos (**8**), IndaBOX (**9**) and Ph-pyBOX (**10**) also resulted in a lack of chiral induction.[16] Based on the chiral counterion approach reported by Toste and coworkers [17] we next investigated the use of the chiral silver phosphate, Ag(*S*)-TRIP (**13**), in the gold-catalysed spirocyclisation of **2**. Surprisingly, spiroacetal **5** was obtained in 82:18 er while only 54:46 er was obtained for spiroacetal **1** (entry 15). A range of chiral phosphine–gold complexes were then used in combination with the chiral silver phosphate counterion. A slight improvement in enantioselectivity for **5** was observed using chiral ligands **6**, **7**, **11** and **12** (entries 16–19), however, no significant enantioselectivity for spiroacetal **1** was observed.

Our focus next turned to optimising the enantioselectivity for spiroacetal **5**. The chiral silver phosphate alone was found to also facilitate the reaction with good enantioselectivity (84:16 er for spiroacetal **5**), but gave spiroacetals **1** and **5** in poor yield (29%) even after extended reaction times (50 h, entry 20). The catalyst loading could be reduced to 2 mol % without significant change



Scheme 2. Synthesis of dihydroxyalkyne **2**. Reaction conditions: (i) $Pd(OAc)_2$, dtbpf, K_2CO_3, NMP, 50 °C, 2 h, 66%; (ii) *p*-TSA (20 mol %), EtOH, 55 °C, 48 h, 77%.

Table 1
Asymmetric gold-catalysed spirocyclisation



Entry	Catalyst[a]	L[b]	AgX[c]	Yield[d]	**1**:**5**[e]	er(**1**)[f]	er(**5**)[f]
1	$PdCl_2$	—	—	97	63:37	—	—
2	$CuBr{\cdot}SMe_2$	—	$AgSbF_6$	25	57:43	—	—
3	AuCl	—	$AgSbF_6$	53	53:47	—	—
4	$AuCl_3$	—	—	92	74:26	—	—
5	$AuPPh_3Cl$	—	—	—	—	—	—
6	$AuPPh_3Cl$	—	AgOTf	75	82:18	—	—
7	$AuPPh_3Cl$	—	$AgSbF_6$	99	77:23	—	—
8	$AuPPh_3Cl$	*rac*-**6**	$AgSbF_6$	83	85:15	—	—
9[g]	$AuPPh_3Cl$	*rac*-**6**	$AgSbF_6$	72	48:52	—	—
10[g]	$AuCl_3$	*rac*-**6**	$AgSbF_6$	81	10:90	—	—
11	$AuPPh_3Cl$	(*S*)-**6**	$AgSbF_6$	98	87:13	0	0
12	$AuPPh_3Cl$	(*R*)-**7**	$AgSbF_6$	76	83:17	0	0
13[h]	$AuPPh_3Cl$	(*S*)-**6**	$AgSbF_6$	—	—	—	—
14[h]	$AuPPh_3Cl$	(*R*)-**7**	$AgSbF_6$	96	94:6	0	0
15	$AuPPh_3Cl$	-	Ag(*S*)-**13**	81	88:12	54:46	82:18
16	$AuCl{\cdot}SMe_2$	(*S*)-**6**	Ag(*S*)-**13**	83	75:25	54:46	86:14
17	$AuCl{\cdot}SMe_2$	(*R*)-**7**	Ag(*S*)-**13**	72	84:16	51:49	87:13
18	$AuCl{\cdot}SMe_2$	(*S*)-**11**	Ag(*S*)-**13**	99	93:7	53:47	87:13[i]
19	$AuCl{\cdot}SMe_2$	(*R*)-**12**	Ag(*S*)-**13**	99	68:32	53:47	86:14
20	—	—	Ag(*S*)-**13**	29	68:32	53:47	84:16
21	$AuCl{\cdot}SMe_2$	(*S*)-**6**	Ag(*S*)-**13**	83	96:4	55:45	86:14
22	$AuCl{\cdot}SMe_2$	(*R*)-**6**	Ag(*S*)-**13**	27	100:0	50:50	—

All reactions carried out in CH_2Cl_2 at rt (unless otherwise noted).
[a] 10 mol % catalyst except 2 mol % for entry 21.
[b] Catalyst:L (2:1).
[c] [M]:AgX (1:1) except entry 10 (1:3).
[d] Isolated yield (%) of regioisomeric mixture.
[e] Determined by ^{1}H NMR.
[f] er determined by chiral HPLC.
[g] 1,4-Dioxane as solvent.
[h] Reaction at −40 °C.
[i] Mixture gave $[\alpha]_D^{25}$ −13 (*c* 1.0, CH_3Cl).

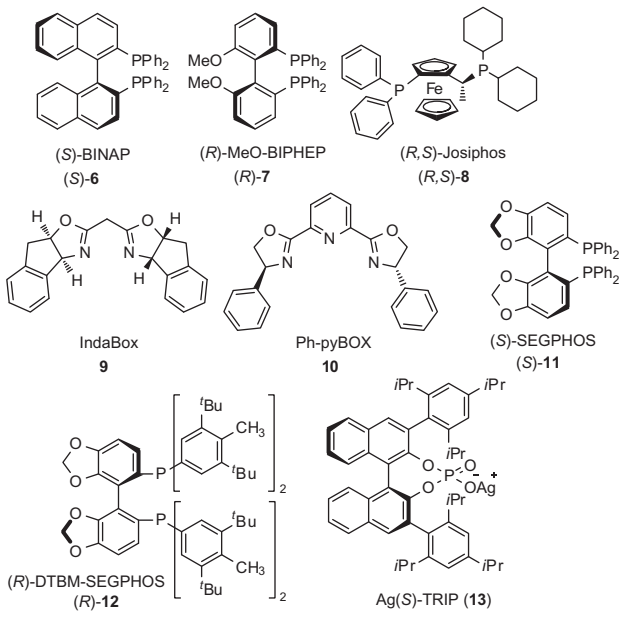


Figure 2. Structures of chiral ligands and counterions.

in enantioselectivity or yield (entry 21). Matched and mismatched pairing was not apparent in our studies with only a 7% difference in er obtained for spiroacetal **1** when pairing Ag(*S*)-TRIP (**13**) with