Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 193–195

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of β-arylbutenolides via palladium(0) catalysed asymmetric coupling cyclisation reaction of racemic allenic carboxylic acids with aryl iodides

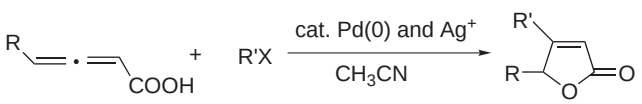
Shengming Ma,* Zhangjie Shi and Shulin Wu

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

Received 27 November 2000; accepted 22 January 2001

Abstract—Bis(oxazoline) **2c** was used as a chiral ligand in the Pd(0) catalysed enantioselective coupling cyclisation of 2,3-allenoic acids with aryl iodides affording butenolides in reasonable yields and with e.e.s of up to 53%.

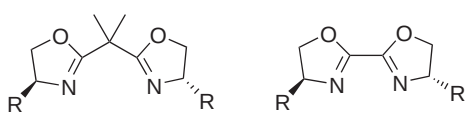
The synthesis of butenolides is of interest to synthetic chemists because of their potential biological activities as well as the wide ranging occurrence of butenolides in natural products.[1] Recently, we have developed some efficient methodologies for the synthesis of butenolides from 2,3-allenoic acids.[2] In particular, polysubstituted butenolides can be produced via the Pd(0)/Ag(I) co-catalysed coupling cyclisation reaction of 2,3-allenoic acids and organic halides (Eq. (1)).[2a] In this reaction, the Pd atom at least partially takes part in the process of the formation of the chiral centre in the butenolide, which led us to investigate the catalytic enantioselective synthesis of butenolides.[3,4] Herein, we wish to report our recent investigations into this asymmetric butenolide synthesis.



(1)

Under our original coupling cyclisation conditions,[2a] when $Pd_2(dba)_3{\cdot}CHCl_3$ and ligand **2c**[5] (Fig. 1) were used instead of $Pd(PPh_3)_4$ as the catalyst at a temperature of 85°C, the reaction between **1a** and iodobenzene afforded the coupling cyclisation product **3a** in 56% yield with zero e.e. (Table 1, entry 1). However, when this reaction was carried out at room temperature, **3a** was isolated in 24% yield and 37% e.e. together with the formation of cycloisomerisation product **3a′** in 60% yield with an e.e. of 7% (Table 1, entry 2). Several reaction conditions were screened, but the results were disappointing (Table 1, entries 2–8). Thus, minimising the cycloisomerisation reaction was necessary to optimise the reaction yield.

The original reaction was heterogeneous as a result of the poor solubility of Ag_2CO_3 and K_2CO_3 in CH_3CN, it is also known that Ag(I) catalyses the cycloisomerisation of 2,3-allenoic acids under certain conditions,[6] thus, a new reaction was developed free of K_2CO_3 and Ag_2CO_3. After screening numerous conditions (Table 1, entries 1–8), we observed that when $(i\text{-Pr})_2NEt$ was used as the base in place of K_2CO_3 and Ag_2CO_3, the reaction afforded the expected product **3a** in moderate yield but with only a trace amount of **3a′**. When the temperature was lowered to −15°C, butenolide **3a** was obtained in 52% yield and 52% e.e. as the sole product (Table 1, entry 9). At this point, 31% of *racemic* **1a** was recovered,[7] indicating that the low yield was caused by incomplete conversion and the reaction is not a kinetic resolution process of the starting 2,3-allenoic acids. It is interesting to observe that when other different bis(oxazoline) ligands **2a**–**2b** and **2d**–**2e**[5] (Fig. 1) were used



2a R = Ph
2b R = *i*-Pr
2c R = Bn

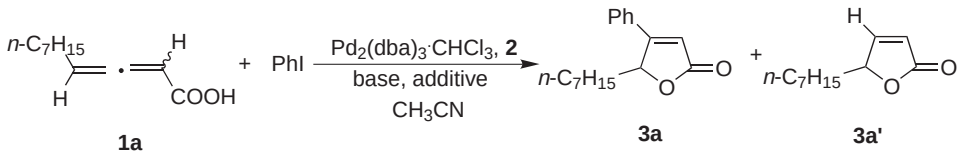
2d R = Ph
2e R = Bn

Figure 1.

* Corresponding author.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00046-5

Table 1. The coupling cyclisation of **1a** and iodobenzene under different conditions[a]

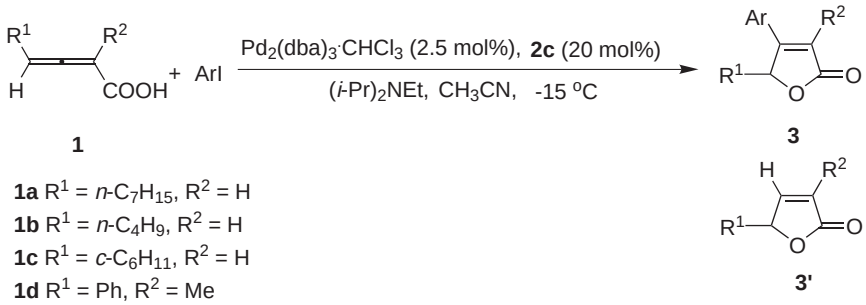


1a **3a** **3a'**

Entry	2	PhI (equiv.)	Base (equiv.)	Additive (mol%)	Temp. (°C)	Time (h)	3a[c,d] % (e.e. %)	3a'[c,d] % (e.e.)
1[b]	**2c**	4	K_2CO_3 (4)	Ag_2CO_3 (5)	85	2	56 (0)	0
2	**2c**	4	K_2CO_3 (4)	Ag_2CO_3 (5)	rt	11	24 (37)	60 (7)
3	**2c**	2	K_2CO_3 (4)	–	rt	11	20 (35)	19 (1.7)
4	**2c**	2	K_2CO_3 (4)	TBAB (100)	rt	12	47 (4)	0
5[b]	**2c**	4	$KHCO_3$ (1)	Ag_2CO_3 (3.6)	rt	10.5	0	0
6[b]	**2c**	4	$KNa(C_4H_4O_6)$ (4)[e]	Ag_2CO_3 (3.6)	rt	10.5	0	0
7[b]	**2c**	4	Cs_2CO_3 (4)	Ag_2CO_3 (3.6)	rt	16	28 (5)	0
8	**2c**	2	$(i\text{-Pr})_2NEt$ (1.2)	–	rt	10	51 (12)	18.1 (1)
9	**2c**	6	$(i\text{-Pr})_2NEt$ (1.2)	–	−15	48	**52 (52)**	0
10	**2a**	3.5	$(i\text{-Pr})_2NEt$ (1.2)	–	−15	96	71 (0)	0
11	**2b**	6	$(i\text{-Pr})_2NEt$ (1.2)	–	−15	55.5	52 (13)	14 (0)
12	**2d**	6	$(i\text{-Pr})_2NEt$ (1.2)	–	−20	55	42 (0)	0
13	**2e**	3.5	$(i\text{-Pr})_2NEt$ (1.2)	–	−15	66	37.5 (2.6)	0

[a] 6 Equiv. of PhI, 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, and 20 mol% of **2** were used unless otherwise stated.
[b] 10 mol% of **2c** was used.
[c] Isolated yield.
[d] E.e.% values were determined by HPLC using an OD chiral column (eluent: *n*-hexane:2-propanol = 9:1).
[e] Sodium potassium tartarate was used as the base.

Table 2. The results of Pd(0) catalysed coupling cyclisation of **1** and aryl iodides



1 **3** **3'**

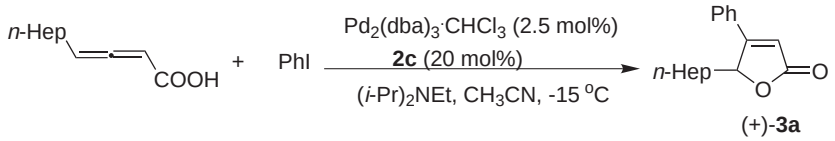
1a $R^1 = n\text{-}C_7H_{15}$, $R^2 = H$
1b $R^1 = n\text{-}C_4H_9$, $R^2 = H$
1c $R^1 = c\text{-}C_6H_{11}$, $R^2 = H$
1d $R^1 = Ph$, $R^2 = Me$

Entry	1	ArI (equiv.)	Time (days)	3[a] (%)	E.e.[b] (%)
1	**1a**	Phenyl (6)	2	**3a** (52)	52
2	**1a**	4-Methylphenyl (4)	2	**3b** (51)	43
3	**1a**	4-Methoxycarbonylphenyl (2)	2	**3c** (52)	49
4	**1a**	4-Methoxyphenyl (2)	2.5	**3d** (53)	47
5	**1b**	Phenyl (6)	2.5	**3e** (47)	50
6	**1b**	4-Methylphenyl (4)	2.5	**3f** (44)	53
7	**1b**	4-Methoxycarbonylphenyl (2)	2.5	**3g** (53)	53
8	**1b**	4-Methoxyphenyl (2)	2.5	**3h** (51)	46
9	**1c**	Phenyl (6)	2.5	**3i** (36)	0
10	**1d**	Phenyl (1.2)	2.5	**3j'** (100)	–

[a] Isolated yield.
[b] E.e.s were determined by HPLC.

instead of **2c** as the ligand in this reaction, the results were poor (Table 1, entries 10–13).

Using these reaction conditions, we examined the behaviour of other substrates (Table 2). We found that the coupling reaction went smoothly with aromatic iodides bearing either electron withdrawing or donating groups, and afforded the corresponding butenolides in similar yields and e.e.s. The length of the carbon chain in the 4-position of the 2,3-allenoic acid was found to



time (h)	yield (%)	e.e. (%)
8	17	47
20	30	51
30	34	52
48	57	51
192	76	29

Scheme 1.

have little effect on the yield and e.e. and additionally, the e.e. can be affected greatly by steric hindrance from the substituent group, such as *c*-hex (Table 2, entry 9). When 2-methyl-4-phenyl-2,3-butenoic acid was used only the cycloisomerisation product **3j′** was formed (Table 2, entry 10).

The e.e. of the product **3a** did not change with lengthened reaction time of 48 hours. However, after 8 days, the reaction afforded (+)-**3a** in a higher yield (76%) but with lower enantioselectivity (29% e.e.) (Scheme 1).

In conclusion, we have developed a silver(I) free reaction for the coupling cyclisation reaction of aromatic iodides and 2,3-allenoic acids.[8,9] Based on this, the first example of the catalytic enantioselective synthesis of β-aryl butenolides was observed. According to the results presented in this paper, the reaction is believed to occur via carbopalladation of the allene to form a π-allyl-palladium intermediate, followed by an enantioselective intramolecular allylic substitution.[2a] Further studies in this area are now being carried out in our laboratory.

Acknowledgements

We thank the National Natural Science Foundation of China (Project No. 29932020) and the Major State Basic Research Development Program (Grant No. G2000077500) for financial support.

References

1. (a) Brima, T. S. US 4,968,817, 1990; *Chem. Abstr.* **1991**, *114*, 185246y; (b) Tanabe, A. Jpn. Kokai. Tokyo. Koho JP. 63,211,276 [88,211,276], 1988; *Chem. Abstr.* **1989**, *110*, 94978; (c) Lee, G. C. M. Eur. Pat. EP. 372,940, 1990; *Chem. Abstr.* **1990**, *113*, 191137j; (d) Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S; Thrien, M. PCT Int. Appl. WO 95,00,501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y; (e) Lee Gary, C. M.; Gast, M. E. PCT Int. Appl. WO. 91 16,055, 1991: *Chem. Abstr.* **1992**, *116*, 59197m.
2. (a) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387; (b) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419; (c) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314; (d) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393; (e) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *40*, 12137.
3. (a) Gawronski, J. K.; van Oeveren, A.; van der Deen, H.; Leung, C. W.; Feringa, B. L. *J. Org. Chem.* **1996**, *61*, 1513; (b) Gawronski, J. K.; Chen, Q.; Geng, Z.; Huang, B.; Martin, M. R.; Mateo, A. I.; Brzostowska, M.; Rychlewska, U.; Feringa, B. *Chirality* **1997**, *9*, 537.
4. For such a reaction with Ag^+, the direct cyclisation catalysed by Ag^+ followed by transmetallation and reductive elimination would make any enantioselective synthesis of butenolides from racemic 2,3-allenoic acids impossible. See Ref. 2a.
5. The ligands **2a**–**2e** were prepared according to the known method: Matt, P. Von; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.
6. (a) Marshall, A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367; (b) Marshall, A.; Bartley, S.; Wallace, M. *J. Org. Chem.* **1996**, *61*, 5729; (c) Marshall, A.; Hinkle, W. *J. Org. Chem.* **1996**, *61*, 4247.
7. Both the yield and e.e. value of **1a** were determined by its conversion to the corresponding ethyl ester via evaporation of the solvent followed by addition of DMF, $(i\text{-Pr})_2$NEt and EtI.
8. Venkruijsse, H. D.; Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes. A Laboratory Manual*; Elsevier: Amsterdam, The Netherlands, 1981; p. 33.
9. Bestmann, H. J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198.