Tetrahedron Letters 51 (2010) 5724–5727

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Application of 3,3′-disubstituted xylBINAP derivatives in inter- and intramolecular asymmetric Heck/Mizoroki reactions

Danica A. Rankic, Daniela Lucciola, Brian A. Keay *

Department of Chemistry, University of Calgary, 2500 University Drive NW Calgary, Alberta, Canada T2N 1N4

ARTICLE INFO

Article history:
Received 9 July 2010
Revised 20 August 2010
Accepted 24 August 2010
Available online 31 August 2010

Keywords:
Heck/Mizoroki reactions
Polyene cyclization
BINAP
3,3′-Disubstitution
3,5-Dialkyl meta effect

ABSTRACT

3,3′-Disubstituted xylBINAP derivatives were applied to inter- and intramolecular asymmetric Heck/Mizoroki reactions. The results from these reactions were compared to those obtained with (*R*)-xylBINAP, (*S*)-BINAP and 3,3′-disubstituted BINAP derivatives. Catalysts derived from 3,3′-disubstituted xylBINAP ligands were found to be most effective in the arylation of 2,3-dihydrofuran in terms of reaction times, conversions, and product enantioselectivity.

The modification of BINAP can be used to improve the enantioselectivity of some asymmetric reactions.[1–3] Notably, 3,3′-disubstituted BINAP and xylBINAP ligands (Chart 1) have been shown to afford superior enantioselectivities in the Rh-catalyzed hydrogenation of dehydroamino acids.[2,3] Recently, our group showcased the effects of 3,3′-disubstitution of BINAP in inter- and intramolecular Heck/Mizoroki reactions.[4] In certain cases, both reversal in the absolute enantiosense of product and enhancements in product enantioselectivities were observed. In this report, we disclose an extension of this work by utilizing 3,3′-disubstituted xylBINAP derivatives (**2b–e**) in inter- and intramolecular Heck/Mizoroki reactions with the aim of assessing how combining 3,3′-disubstitution with the 3,5-dialkyl meta effect[5,6] influences the enantioselectivity of these reactions.

The first reaction that we investigated was the cyclization of aryl triflate **3** to polycycle **4**, involving two consecutive Heck/Mizoroki cyclizations. Hopkins et al. demonstrated that substituting the 3 and 3′ positions of BINAP did not result in any improvements with regard to enantioselectivity in the cyclization of triflate **3**.[4] The best enantioselectivity obtained was with (*S*)-3,3′-(OiPr)$_2$-BINAP (**1c**), which gave the cyclization adduct (*R*)-**4** in 74% ee (Table 1, entry 3). Note that an enantiosense switch was observed upon installation of groups in the 3,3′-positions of BINAP; (*S*)-BINAP provided (*R*)-product whereas (*S*)-3,3′-substituted BINAP ligands provided (*S*)-product. This enantiosense reversal has also been observed when certain 3,3′-disubstituted MeO-BIPHEP ligands have been utilized in the cyclization of triflate **3** to polycycle **4**.[7,8] The OMe- and OPiv-substituted BINAP ligands **2b** and **2e** performed quite poorly in this reaction, affording tetracycle **4** in 0% and 14% ee, respectively (entries 2 and 4).

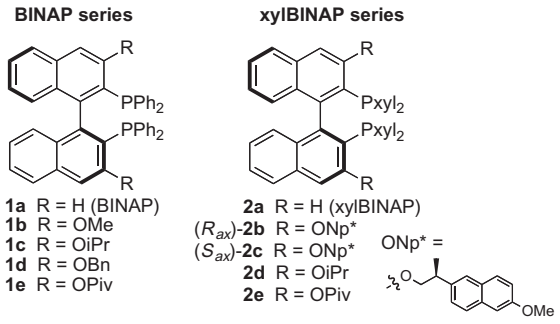


Chart 1. 3,3′-Disubstituted BINAP and xylBINAP derivatives.

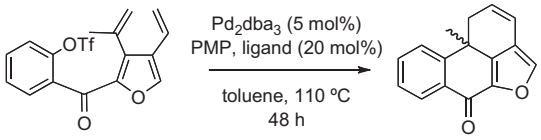
When (*R*)-xylBINAP (**2a**) was used in the polyene cyclization of **3**, the enantiomeric excess of the product **4** was reduced by approximately 40% in comparison with (*S*)-BINAP, representative of a strongly negative 3,5-dialkyl meta effect[9,10] (Table 1, entry 1 vs entry 6). However, the use of a BINAP ligand containing *P*-xylyl groups instead of *P*-phenyl groups did not result in a reversal of product enantiosense; product (*R*)-**4** was obtained from (*R*)-xylBINAP. This is in contrast to what was observed when xylBINAP was used in the hydrogenation of dehydroamino acid derivatives.[3]

The use of 3,3′-disubstituted xylBINAP ligands in the cyclization of **3** to **4** led to slight improvements in selectivity over those observed with xylBINAP. However, the high enantioselectivities seen with (*S*)-BINAP and 3,3′-disubstituted BINAP ligand **1c** were not

* Corresponding author. Tel.: +1 403 220 3293; fax: +1 403 289 9488.
E-mail address: keay@ucalgary.ca (B.A. Keay).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.078

Table 1
Asymmetric Pd-catalyzed intramolecular Heck/Mizoroki cyclization of polyene **3** to tetracycle **4**

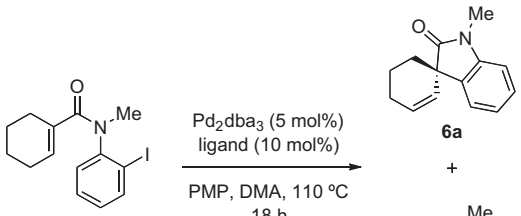


3 **4**

Entry[a]	Series	Ligand	3,3′-Group	Yield (%)	%ee (config)[b]
1[c]	BINAP	(*S*)-**1a**	H	88	72 (*S*)
2[c]		(*S*)-**1b**	OMe	0	—
3[c]		(*S*)-**1c**	OiPr	93	74 (*R*)
4		(*S*)-**1d**	OBn	84	46 (*R*)
5[c]		(*S*)-**1e**	OPiv	73	14 (*R*)
6	xylBINAP	(*R*)-**2a**	H	42	28 (*R*)
7		(R_{ax})-**2b**	ONp*	90	29 (*S*)
8		(S_{ax})-**2c**	ONp*	77	47 (*R*)
9		(*R*)-**2d**	OiPr	88	40 (*S*)

[a] All catalysts were generated in situ by premixing Pd_2dba_3 and ligand for 30 min at rt in toluene.
[b] Measured by HPLC (9:1 hexanes/*i*PrOH, 1.0 mL/min, Chiralcel OD column).
[c] Obtained from Ref. 4 for the purposes of comparison.

Table 2
Asymmetric Pd-catalyzed intramolecular Heck/Mizoroki reaction of iodoaniline **5** to 3,3′-spirooxindoles **6a** and **6b**



5

Entry[a]	Series	Ligand	3,3′-Group	**6a**:**6b**	%ee (config)[b]
1	BINAP[c]	(*S*)-**1a**	H	1.1:1	84 (*S*)
2		(*S*)-**1b**	OMe	2.6:1	11 (*R*)
3		(*S*)-**1c**	OiPr	2.0:1	19 (*R*)
4		(*S*)-**1d**	OBn	1.2:1	12 (*R*)
5		(*S*)-**1e**	OPiv	1.4:1	1 (*S*)
6	xylBINAP	(*R*)-**2a**	H	1.5:1	28 (*R*)
7		(R_{ax})-**2b**	ONp*	1.2:1	10 (*S*)
8		(S_{ax})-**2c**	ONp*	1:1.6	2 (*S*)
9		(*R*)-**2d**	OiPr	1:1.5	8 (*S*)

[a] All catalysts were generated in situ by premixing Pd_2dba_3 and ligand for 30 min at 60 °C in DMA.
[b] Measured by HPLC (9:1 hexanes/*i*PrOH, 1.0 mL/min, Chiralcel OD column).
[c] Obtained from Ref. 4 for the purposes of comparison.

achieved with this series of ligands. Ligand (S_{ax})-**2c** outperformed all others in the xylBINAP series, providing tetracycle (*R*)-**4** in 47% ee (Table 1, entry 8). Related diphosphine (R_{ax})-**2b** provided the product in an enantioselectivity comparable to (*R*)-xyBINAP (entries 6 and 7). Tetracycle **4** was generated in 40% ee when (*R*)-3,3′-$(OiPr)_2$-xylBINAP (**2d**) was used, representing a reduction in enantiomeric excess in comparison with its BINAP counterpart (*S*)-**1c** (entry 3 vs entry 9). This indicated that the effects from 3,3′-disubstitution and the 3,5-dialkyl meta effect are not cooperative in the case of the Heck/Mizoroki cyclization of **3** to **4**. The attenuation of enantioselectivity when either 3,3′-disubstitution or *P*-xylyl groups are present on a BINAP ligand may be due to a weak interaction between the metal and substrate due to the excessive steric bulk present in the catalytic pocket.[11]

When a catalyst derived from (*S*)-BINAP and Pd_2dba_3 was used to promote the cyclization of iodoaniline **5**, developed by Overman and co-workers,[12] products **6** were obtained in 84% ee, as predominantly the (*S*)-enantiomer (Table 2, entry 1). Moreover, cyclization products **6** were isolated as a mixture of double bond isomers in a 1.1:1 ratio, as measured by HPLC.[4] The substitution of the 3 and 3′ positions of BINAP was not found to be an effective strategy for increasing the enantioselectivity of the cyclization of **5**. The best result for the substituted BINAP ligands was obtained with OiPr-substituted BINAP ligand (*S*)-**1c**, which provided the product (*R*)-**6** in 18.9% ee (entry 3). In all cases but one, (*S*)-3,3′-disubstituted BINAP derivatives provided spirocycles **6** in the opposite configuration than that provided by (*S*)-BINAP; (*S*)-BINAP provided (*S*)-product and (*S*)-3,3′-disubstituted BINAP ligands provided (*R*)-product (entries 2–4).

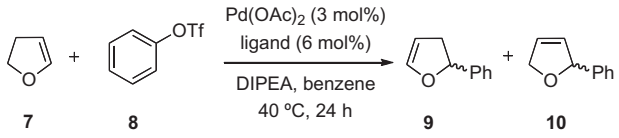
Although 3,3′-disubstitution of the BINAP skeleton failed to improve the enantioselectivity of this cyclization, it did succeed in increasing the preference for one double bond isomer over the other. The best ratio was obtained with OMe-disubstituted BINAP **1b**, which afforded a 2.6:1 ratio of double bond isomers, bettering the 1.1:1 ratio obtained with BINAP (entry 2).[4]

All ligands belonging to the xylBINAP series failed to surpass BINAP in the Pd-catalyzed cyclization of iodoanilide **5** to form spirooxindoles **6**. Parent ligand (*R*)-xylBINAP outperformed all 3,3′-disubstituted xylBINAP ligands, affording product (*R*)-**6** in 28% ee as a 1.5:1 mixture of double bond isomers (Table 2, entry 6). Naproxen ether-substituted 3,3′-disubstituted xylBINAP (R_{ax})-**2b** afforded spirocycles (*S*)-**6** in 10% ee, demonstrating the same enantiosense reversal observed in the cases of 3,3′-disubstituted BINAP ligands **1b–d**. The diastereomer of (R_{ax})-**2b**, (S_{ax})-**2c**, afforded racemic product and OiPr-substituted xylBINAP (*R*)-**2d** gave (*S*)-product **6** in 8% ee. This represents less than half the product ee that was afforded by the related 3,3′-disubstituted BINAP (*R*)-**1c**. Interestingly, (S_{ax})-**2c** and (*R*)-**2d** caused the ratio of the double bond isomers to switch, in favor of isomer **6b**.

The intermolecular arylation of 2,3-dihydrofuran (**7**) catalyzed by a Pd/(*S*)-BINAP catalyst system afforded phenyl-substituted dihydrofurans **9** and **10** in a 91:9 ratio and in 32% conversion (Table 3, entry 1).[4] Phenylated dihydrofuran **9** was produced as predominantly the (*S*)-enantiomer in 66% ee. Its double bond isomer **10** was determined to be enriched in the (*R*)-enantiomer with 57% ee. The configurations of products **9** and **10** obtained with 3,3′-disubstituted BINAP derivatives **1b–e** were consistent with the product configurations obtained with (*S*)-BINAP. Hopkins et al. found that product ratios also improved upon 3,3′-disubstitution of the BINAP scaffold, with ligands **1b–e** providing anywhere from 96:4 up to 99:1 ratios of **9** to **10**.[4] In two instances, 3,3′-disubstitution also improved the enantioselectivity of the major product **9**. OiPr- and OPiv-substituted BINAP derivatives **1c** and **1e** gave arylated dihydrofuran **9** in 73% ee and 80% ee, respectively (entries 3 and 5). Isomer **10**, however, was produced in a much lower ee in reactions involving **1c** and **1e** than with the parent BINAP.

The use of a Pd/(*S*)-xylBINAP catalyst system resulted in a drastic change in product ratios in comparison with (*S*)-BINAP (Table 1, entry 6). (*S*)-BINAP provided the mixture of arylated dihydrofurans **9** and **10** in a 91:9 ratio but using (*S*)-xylBINAP changed this ratio to 66:34. Interestingly, the ee of isomer **9** decreased considerably in comparison with the BINAP system, yet isomer **10** was produced with greater enantiomeric excess (83%). The stereochemical preference was maintained for both isomers. In other words 2,3-dihydrofuran **9** was produced predominantly as the (*S*)-enantiomer and 3,4-dihydrofuran **10** were produced predominantly as the

Table 3
Asymmetric Pd-catalyzed intermolecular arylation of 2,3-dihydrofuran (7) with phenyltriflate (**8**)



7 **8** **9** **10**

Entry[a]	Series	Ligand	3,3′-Substituent	Conversion (%)	Product ratio (%ee, config)[b]	
					9	**10**
1	BINAP[c]	(*S*)-**1a**	H	32	91 (66, *S*)	9 (57, *R*)
2		(*S*)-**1b**	OMe	56	99 (7, *S*)	1 (22, *R*)
3		(*S*)-**1c**	OiPr	100	99 (73, *S*)	1 (2, *R*)
4		(*S*)-**1d**	OBn	100	97 (40, *S*)	3 (16, *R*)
5		(*S*)-**1e**	OPiv	68	96 (80, *S*)	4 (16, *R*)
6	xylBINAP	(*S*)-**2a**	H	100	66 (21, *S*)	34 (83, *R*)
7		(R_{ax})-**2b**	ONp*	100	98 (90, *R*)	2 (45, *R*)
8		(S_{ax})-**2c**	ONp*	100	98.5 (>99, *S*)	1.5 (77, *S*)
9		(*R*)-**2d**	OiPr	100	99 (83, *R*)	1 (6, *S*)

[a] All catalysts were generated in situ by premixing $Pd(OAc)_2$ and ligand for 30 min at rt in benzene.
[b] Measured by chiral GC (80 °C for 2 min, increase 1 °C/min for 38 min. Cyclodex-B column).
[c] Obtained from Ref. 4 for the purposes of comparison.

(*R*)-enantiomer.Upon substitution of the 3 and 3′ positions of xylBINAP, improvements in both product ratio and enantioselectivities were achieved (Table 3, entries 7–9). The OiPr-substituted xylBINAP **2d** outperformed its BINAP counterpart **1c**, affording product **9** in 83% ee instead of 73% ee, however the product ratios and enantioselectivity of product **10** were comparable between the two ligands (entry 9). This seemed to indicate that the effects of 3,3′-disubstitution and the 3,5-dialkyl meta effect operate synergistically in the case of ligand **2d** and for this reaction type. The most impressive results were obtained with diastereomeric ligands (R_{ax})-**2b** and (S_{ax})-**2c**. Both afforded product **9** nearly exclusively (98:2 ratio of **9** to **10**). Moreover, catalysts based on these ligands afforded the highest ee's for any 3,3′-disubstituted BINAP or xylBINAP ligands. (R_{ax})-**2b** gave arylated 2,3-dihydrofuran (*R*)-**9** in 90% ee and (S_{ax})-**2c** provided product (*S*)-**9** in >99% ee (*S*) (entries 7 and 8). Note that 3,4-dihydrofuran arylation product **10** was also produced with the same sense of chirality as the configuration of the ligand used in both cases, with moderate enantioselectivities of 45% ee and 77% ee obtained using (R_{ax})-**2b** and (S_{ax})-**2c**, respectively.

The fact that arylation products **9** and **10** were produced with same absolute configuration when ligands (R_{ax})-**2b** and (S_{ax})-**2c** were utilized in the Pd-catalyzed arylation of 2,3-dihydrofuran provides important mechanistic insight into the intermolecular Heck/Mizoroki arylation of 2,3-dihydrofuran (**7**). Although not well understood, it was originally proposed that the mechanism of this intermolecular Heck/Mizoroki reaction proceeds via a kinetic resolution.[13] The evidence for this was a connection between the product ratio and enantiomeric purity of **9**. Hayashi and co-workers observed that as the ratio of **10** to **9** increased, the enantiomeric excess of **9** increased as well. Their best results for the enantioselectivity of **9** were obtained when $Pd(OAc)_2$ was used as a precatalyst and Proton Sponge™ was used as a base instead of DIPEA. They received a **9**:**10** ratio of 71:29 with **9** being produced in >96% ee and **10** being produced in 17% ee *after a reaction time of 216 h (9 days)*. They postulated that if the coordination of 2,3-dihydrofuran (**7**) to the Pd/(*S*)-BINAP catalyst after oxidative addition of phenyl triflate (**8**) occurred via the pro-*S* face, the resulting metal alkyl was capable of undergoing a β-hydride elimination/re-insertion/β-hydride elimination sequence to produce **9**. Conversely, they thought that if coordination of 2,3-dihydrofuran occurred via the pro-*R* face of the olefin, the migratory insertion product underwent a single, facile β-hydride elimination to eject (*R*)-product **10**. This explanation accounted for why arylated dihydrofuran **9** was always produced with the (*S*)-configuration and **10** was always produced with the (*R*)-configuration when (*S*)-BINAP was used as a ligand in this reaction.

In our study, when diastereomeric 3,3′-disubstituted xylBINAP ligands (R_{ax})-**2b** and (S_{ax})-**2c** were used, the absolute configuration of the chiral axis was directly transferred to *both* the arylated products, compounds **9** and **10**. Moreover, high enantiomeric excesses of product **9** could be accessed even when minute amounts of the minor isomer **10** were produced. These two pieces of evidence appear to contradict the kinetic resolution argument put forth by Hayashi and co-workers. We are currently investigating this phenomenon and the results will be reported in a subsequent publication.

In conclusion, we have demonstrated that the incorporation of 3,5-(dimethylphenyl) groups on phosphorus in combination with 3,3′-substituents on the BINAP framework was not beneficial for intramolecular Heck/Mizoroki reactions. However, when an intermolecular Heck/Mizoroki reaction was performed, that is, the arylation of 2,3-dihydrofuran, superior ee's, and conversions were observed in comparison with 3,3′-disubstituted BINAPs and the parent BINAP. Most notably we observed an interesting phenomenon when diastereomeric 3,3′-diastereomeric xylBINAP ligands (R_{ax})-**2b** and (S_{ax})-**2c** were utilized. With these ligands, we found that this reaction proceeded with high enantioselectivity and high specificity for the major isomer **9**, even with comparatively shorter reaction times than those reported by Hiyashi and co-workers[13] (24 h vs 216 h, vide supra). The small amount of isomer **10** that was generated was found to be of the *same configuration* as isomer **9**, which is in contrast to what was previously observed with BINAP. This suggests that the Heck/Mizoroki reaction might not proceed via a kinetic resolution when (R_{ax})-**2b** and (S_{ax})-**2c** are used as ligands for the arylation of 2,3-dihydrofuran. We propose that this might be due to an interaction between the naproxen ether substituents and the aryl triflate upon oxidative addition. We have evidence for a similar interaction in the Rh-catalyzed asymmetric hydrogenations of dehydroamino acids which will be reported elsewhere in due course.

Acknowledgments

The University of Calgary and the Natural Science and Engineering Council of Canada (NSERC) are thanked for funding. D.A.R. and D.L. authors thank both NSERC and Alberta Ingenuity Fund for studentships. Thanks are also extended to Professor Warren Piers for use of his chiral HPLC.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.078.

References and notes

1. Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, 105.
2. Hopkins, J. M.; Dalrymple, S. A.; Parvez, M.; Keay, B. A. *Org. Lett.* **2005**, *7*, 3765.
3. Rankic, D. A.; Hopkins, J. M.; Parvez, M.; Keay, B. A. *Synlett* **2009**, 2513.
4. Hopkins, J. M.; Gorobets, E.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Synlett* **2006**, 3120.
5. Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315.
6. Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670.
7. Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597.
8. Gorobets, E.; Wheatley, B. M. M.; Hopkins, J. M.; McDonald, R.; Keay, B. A. *Tetrahedron Lett.* **2005**, *46*, 3843.
9. Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Magn. Reson. Chem.* **2002**, *40*, 653.
10. Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249.
11. Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560.
12. Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.
13. Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguichi, K. *Organometallics* **1993**, *12*, 4188.