ORGANIC LETTERS

2006
Vol. 8, No. 7
1483−1485

Diastereospecific Intramolecular Ullmann Couplings: Unique Chiral Auxiliary for the Preparation of 3,3′-Disubstituted MeO-BIPHEP Derivatives

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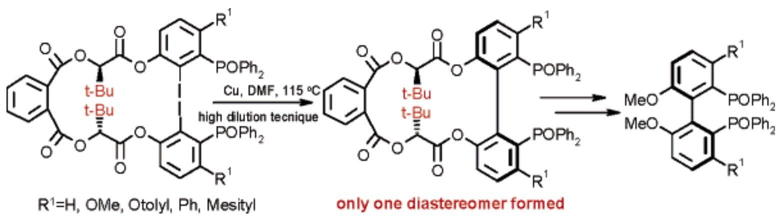
Received February 26, 2006

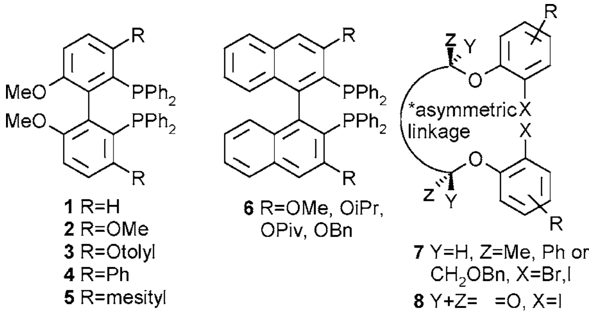
ABSTRACT



A chiral auxiliary is described that provides only one diastereomer during *intra*molecular Ullmann couplings. Treatment of five Ullmann coupling precursors with Cu powder in DMF at 115 °C provides 2,2′,3,3′,6,6′-hexasubstituted 1,1′-biphenyls as single diastereomers in yields ranging from 66% to 91%.

One of the most powerful methods for the preparation of enantiomerically enriched compounds is catalytic asymmetric synthesis. The design and synthesis of chiral bisphosphine ligands is an important area of research toward developing highly enantioselective transition-metal-catalyzed asymmetric reactions.[1] Given that subtle steric and/or electronic perturbations of a ligand can dramatically affect the catalytic activity and selectivity,[2,3] we embarked on a program to prepare 3,3′-disubstituted MeO-BIPHEP[4] (**1**−**5**) and BINAP[5] (**6**) derivatives (Scheme 1). Since the original preparation of MeO-BIPHEP (**1**) involved a cumbersome resolution step by co-crystallization with dibenzoyl-L-tartaric acid[6] that did not work on some of our 3,3′-substituted MeO-BIPHEP deriva-

Scheme 1



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(1) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(2) (a) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 857.

(3) (a) Chen, Y.; Yekta, S.; Yudin, A. *Chem. Rev.* **2003**, *103*, 3155. (b) Kočovský, P.; Vyskočyl, S.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3213. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (d) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.

(4) (a) Gorobets, E.; Wheatley, B. M. M.; Hopkins, J. M.; McDonald, R.; Keay, B. A. *Tetrahedron Lett.* **2005**, *46*, 3843. (b) Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M. R.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597.

(5) Hopkins, J. M.; Dalrymple, S. A.; Parvez, M.; Keay, B. A. *Org. Lett.* **2005**, *7*, 3765.

(6) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

10.1021/ol060484p CCC: $33.50

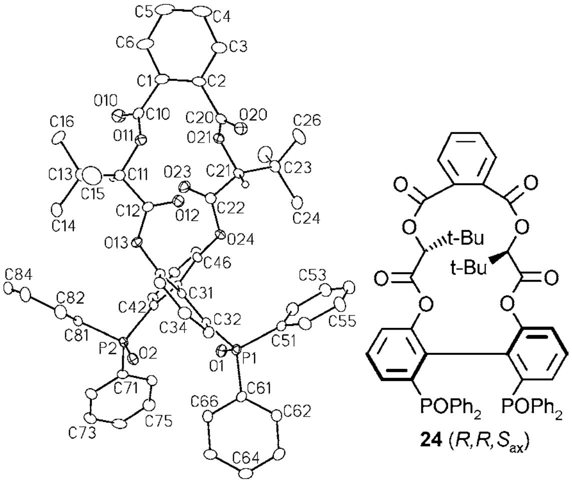
tives, we developed resolutions for these 3,3′-derivatives using L-menthol-Me$_2$SiCl[4b] and (*S*)-2-acetoxypropanoyl chloride.[4a] In both cases, the resulting diastereomers were separated on silica gel. In the latter case, the chiral auxiliary (CA) was attached to a precursor such that diastereomers were formed after an *inter*molecular Ullmann coupling (UC).[7] Since the de's were low (1.1 to 2:1) and some of diastereomers did not separate well on silica gel, we decided to investigate whether a highly diastereoselective *intra*molecular UC could be designed so that the diastereomers would not need to be separated. We herein report a new CA for the preparation of **1**−**5** that provides one diastereomer after an *intra*molecular UC.

A survey of the literature[8] on successful diastereoselective intramolecular UC involving ether linkages **7** indicated that although the % de in some cases were very high (100% de),[9] the yields were moderate to good (54−78%),[10,11] and harsh conditions (e.g., BBr$_3$) were necessary to cleave some of the ether bridges. We decided to take a different tack involving the design of an asymmetric linkage that would involve esters **8** (Scheme 1) rather than ethers **7** such that cleavage of the asymmetric linkage would occur under milder reaction conditions. Although this scenario would place the stereogenic centers within the linkage further away from the newly formed axis of chirality, we were encouraged by some recent findings in which very high % de's were reported in oxidative biaryls couplings[12] in which the stereogenic centers were up to 8 atoms removed[13] from the axis of chirality.

We decided to start with the preparation of MeO-BIPHEP (**1**) as a model, and the first CA used, **9**, was easily prepared from tartaric acid. Using our optimized reaction conditions for intramolecular UC,[14] compound **13** gave mainly deiodized starting material (SM) (48%) and a very small amount of **21** (Table 1). Changing the CA to lactate derivative **10** in which the alcohol groups of the lactates were linked via a succinate (i.e., **14**) provided Ullmann-coupled product **22** in 69% yield with a 71% de. It was felt that if the flexibility in the CA chain was reduced that amount of dehalogenized material would be minimized as the two aromatic rings would be held in closer proximity to one another. Indeed, reducing the degrees of freedom of rotation in the CA linkage by modifying the succinate to a phthalate **11** gave precursor **15** that furnished UC product **23** with a gratifying 95% de (81% yield).[15] Finally, changing the CA from a lactate to the more bulky (*R*)-2-hydroxy-3,3-dimethylbutyrate **16**[16] provided only one diastereomer **24** (>99% de by ^{1}H NMR) in 88% yield. The absolute configuration of the newly formed axis of chirality in **24** was found to be S_{ax} from the X-ray crystal structure (Figure 1). Compounds **16**−**20** were synthesized in excellent yields over five steps starting from (*R*)-2-hydroxy-3,3-dimethylbutanoic acid **29**[16] via diacid **30** (bottom of Scheme 2).

Table 1. Products Ratios from the Intramolecular UC of Compounds **9**−**17**

sm	deiodized sm/UC product (config)	UC product (% isolated yield)	% de
(*R*,*R*)-**13**	95:5 (nd)	**21** (nd)	
(*S*,*S*)-**14**	23:77 (R_{ax})	**22** (69)	71
(*S*,*S*)-**15**	10:90 (R_{ax})	**23** (81)	95
(*R*,*R*)-**16**	9:91 (S_{ax})	**24** (88)	>99
(*R*,*R*)-**17**	4:96 (S_{ax})	**25** (91)	>99
(*R*,*R*)-**18**	17:83 (S_{ax})	**26** (79)	>99
(*R*,*R*)-**19**	6:94 (S_{ax})	**27** (84)	>99
(*R*,*R*)-**20**	21:79 (S_{ax})	**28** (66)	>99



24 (*R*,*R*,S_{ax})

Figure 1. X-ray crystal structure of (*R*,*R*,S_{ax})-**24**. The hydrogen atoms have been removed for clarity.

To determine if the CA derived from (*R*)-2-hydroxy-3,3-dimethylbutyrate would provide high % de's when the 3 and 3′ positions were substituted, compounds **17**−**20** were prepared and subjected to the intramolecular UC. In all four cases, the products **25**−**28** were formed with >99% de (by ^{1}H NMR) in yields ranging from 66 to 91% (Table 1). After

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[7] Qiu, L.; Qi, J.; Pai, C.-C.; Chan, S.; Zhou, Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 4599.

[8] (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

[9] (a) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *J. Am. Chem. Soc.* **1993**, *115*, 9276. (b) Lipshutz, B. H.; Müller, P.; Leinweber, D. *Tetrahedron Lett.* **1999**, *40*, 3577.

[10] Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 649.

[11] Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5815.

[12] Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297.

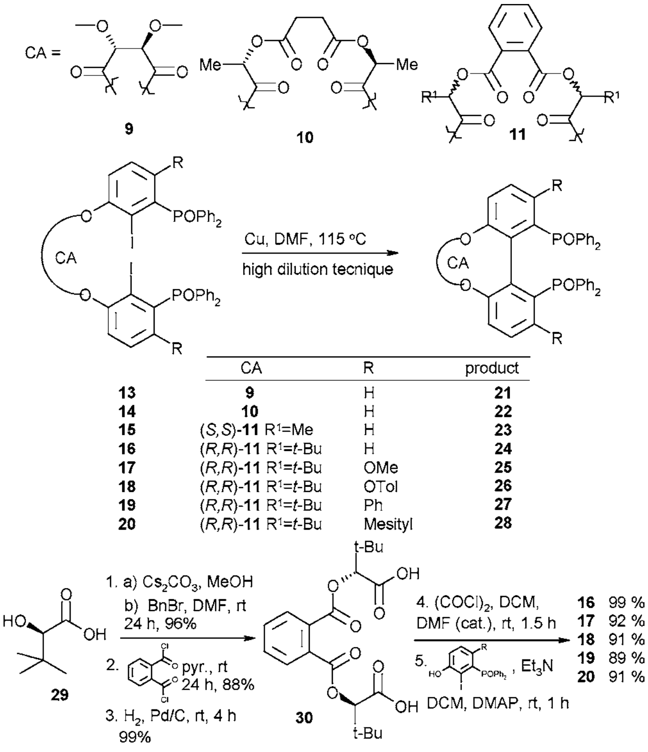
[13] Lipshutz, B. H.; James, B.; Vance, S.; Carrico, I. *Tetrahedron Lett.* **1997**, *38*, 753.

[14] For intramolecular UCs, we found that the amount of deiodized material could be minimized by the addition of the SM (1 mmol in 25 mL of DMF) via syringe pump (4.1 mL/h) to a suspension of 2.7 equiv of Cu powder in DMF (25 mL) preheated to 115 °C.

[15] It is interesting to note that the corresponding *inter*molecular UC using 6-((*R*)-2-acetoxy-propionyloxy)-2-(diphenylphosphinoyl)-1-iodobenzene afforded a 2:1 mixture of diastereomers.[4a]

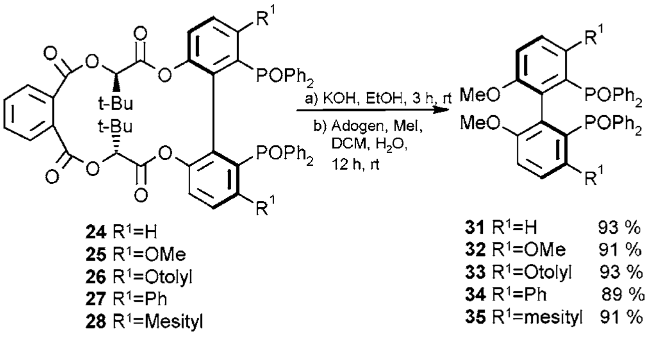
[16] For the preparation and resolution of (*R*)- and (*S*)-2-hydroxy-3,3-dimethylbutanoic acid, see: Kontos, Z.; Huszthy, P.; Bradshaw, J. S.; Izatt, R. M. *Tetrahedron: Asymmetry* **1999**, *10*, 2087.

Scheme 2



	CA	R	product
13	**9**	H	**21**
14	**10**	H	**22**
15	(*S*,*S*)-**11** R^1=Me	H	**23**
16	(*R*,*R*)-**11** R^1=*t*-Bu	H	**24**
17	(*R*,*R*)-**11** R^1=*t*-Bu	OMe	**25**
18	(*R*,*R*)-**11** R^1=*t*-Bu	OTol	**26**
19	(*R*,*R*)-**11** R^1=*t*-Bu	Ph	**27**
20	(*R*,*R*)-**11** R^1=*t*-Bu	Mesityl	**28**

Scheme 3



separation of UC products from deiodized SM and other impurities (silica gel column), the ^{1}H NMR spectrum of major spot showed the presence of only one diastereomer in all cases. Compounds **24**−**28** were then converted into optically pure phosphine oxides **31**−**35** in high yields (Scheme 3).

For additional confirmation that only one diastereomer was formed from the UC and that the minor diastereomer was not lost on the silica gel column mentioned above to remove the deiodized SM and other impurities, the crude UC reaction mixtures containing **24**, **25,** or **26**, after removing the copper salts, were treated with KOH/EtOH followed by methylation with MeI as shown in Scheme 3. Note that upon removal of the CA, any mixture of diastereomers formed in the UC would now become a mixture of enantiomers (i.e., a scalemic mixture). Separation of the possible scalemic mixture of phosphine oxides **31**, **32**, or **33** from the deiodized SM was successful via a silica gel column. The enantiopurity of **31**, **32**, or **33** was then determined by measuring the ^{1}H NMR spectrum in the presence of (−)-(2*R*,3*R*)-dibenzoyltartaric acid.[17] In all cases, only one methoxy signal was observed, indicating the sample was enantiopure. Thus, only one diastereomer was formed during the UC reaction.

In summary, we have designed and synthesized a novel chiral auxiliary that provides only one diastereomer in the intramolecular UC leading to BIPHEP derivatives. The auxiliary is easily prepared and removed after the UC and should be useful toward the asymmetric synthesis of the ellagitannin class of natural products.[18]

Acknowledgment. We thank Merck Frosst Canada, the NSERC CRD program, and the University of Calgary for financial support.

Supporting Information Available: Experimental preparations for **32**−**35**, **16**−**20**, and **24**−**28** are provided along with all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Gorobets, E.; Parvez, M.; Wheatley, B. M. M.; Keay, B. A. *Can. J. Chem.* **2006**, *84*, in press.

(18) (a) Khanbabaee, K.; van Ree, T. *Synthesis* **2001**, 1585. (b) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475. (c) Khanbabaee, K.; van Ree, T. *Nat. Prod. Rep.* **2001**, *18*, 641.