Novel *Cinchona* alkaloid derived ammonium salts as catalysts for the asymmetric synthesis of β-hydroxy α-amino acids via aldol reactions

Bing Ma, Jared L. Parkinson and Steven L. Castle*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602, USA

Abstract—Using the cinchonidine-derived phase-transfer catalyst developed by Park and Jew as a lead structure, we have prepared novel chiral ammonium salts and investigated their efficacy for the preparation of β-hydroxy α-amino acids via asymmetric aldol reactions. The modifications were performed at C3 of the cinchonidine nucleus and include dimers as well as catalysts possessing electron-deficient alkyne and alkene moieties. Some of the new catalysts yielded improvements relative to the Park–Jew catalyst in the aldol reaction.
© 2007 Elsevier Ltd. All rights reserved.

Quaternary ammonium salts derived from inexpensive and readily available *Cinchona* alkaloids have shown great utility as chiral phase-transfer catalysts, particularly in asymmetric alkylations.[1] Recently, we examined the viability of these catalysts for the synthesis of β-hydroxy α-amino acids via aldol reactions, a topic first explored by Miller and Gasparski.[2,3] We discovered that the *N*-2,3,4-trifluorobenzyl-substituted hydrocinchonidine derivative of Park and Jew[4] afforded protected β-hydroxy α-amino acids in good yields under homogenous conditions in conjunction with the phosphazene base *tert*-butyliminotri(pyrrolidino)-phosphorane (BTTP, Scheme 1).[5] Although the *syn* diastereomers were obtained in good ee, the reaction exhibited negligible diastereoselectivity. In an attempt to improve the selectivity of the aldol reaction, we designed novel cinchonidine-based monomeric and dimeric quaternary ammonium salts that retain the 2,3,4-trifluorobenzyl group of the Park–Jew catalyst. In this Letter, we report the synthesis of these catalysts as well as their performance in the aldol reaction.

We viewed the C3-vinyl group of cinchonidine as a potential handle for the construction of new catalysts. Modifications of this functional group such as dehydrogenation,[6] hydroformylation,[7] and oxidative cleavage[8] are known; however, to the best of our knowledge, none of these protocols have been incorporated into the synthesis of quaternary ammonium salt catalysts. Hoffmann and Frackenpohl recently reported that C3-ethynyl *Cinchona* alkaloids are significantly more basic and polar than the parent compounds, thereby demonstrating that this functional group, although remote from the nitrogen, has a profound effect on its properties.[9] Accordingly, we were optimistic that the catalytic abilities of cinchonidine-derived ammonium salts could be tuned via appropriate modifications of the C3-vinyl group. In an attempt to develop catalysts capable of forming tight ion pairs with enolates, we targeted ammonium salts with electron-deficient substituents at this site.
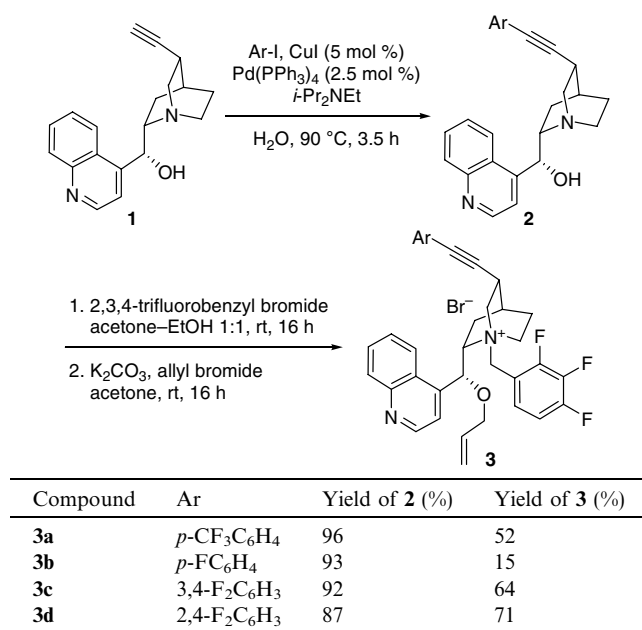
The preparation of C3-alkynyl ammonium salts **3a**–**d** possessing fluorinated and trifluoromethylated aryl groups is summarized in Table 1. We employed
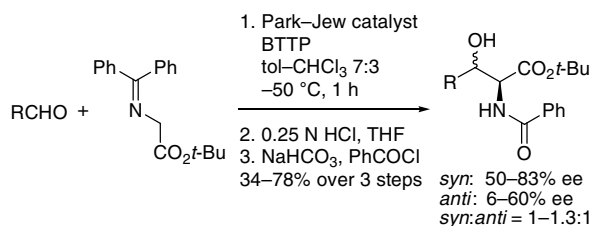
Scheme 1. Asymmetric aldol reaction mediated by Park–Jew catalyst.

Keywords: *Cinchona* alkaloids; β-Hydroxy α-amino acids; Sonogashira coupling; Heck reaction; Asymmetric aldol reaction.
* Corresponding author. Tel.: +1 801 422 1780; fax: +1 801 422 0153; e-mail: scastle@chem.byu.edu

Table 1. Synthesis of C3-alkynyl ammonium salts **3a–d**

Compound	Ar	Yield of **2** (%)	Yield of **3** (%)
3a	*p*-CF$_3$C$_6$H$_4$	96	52
3b	*p*-FC$_6$H$_4$	93	15
3c	3,4-F$_2$C$_6$H$_3$	92	64
3d	2,4-F$_2$C$_6$H$_3$	87	71

10,11-didehydrocinchonidine (**1**)[6a] as our starting material, and after considerable experimentation discovered that the aqueous Sonogashira coupling conditions of Bhattacharya and Sengupta[10] were optimal for the preparation of arylated compounds **2**. Then, N-benzylation followed by O-allylation afforded the target compounds in good yield, with the exception of *p*-fluorophenyl-substituted salt **3b**. In all cases, benzylation provided the quaternary ammonium salt in essentially quantitative yield without the need for further purification. Thus, the variability in the yields of **3** was a consequence of the O-allylation. Attempts to optimize the allylation in the synthesis of **3b** were unsuccessful.

Unfortunately, despite examining numerous conditions, we were unable to perform the O-allylation on substrates possessing nitroaryl groups. Consequently, the order of steps was changed, and the Sonogashira coupling was performed last in the construction of nitro-containing catalysts **3e–g** (Table 2). Benzylation and allylation of **1** proceeded under the same conditions shown in Table 1 for Sonogashira adduct **2**, affording quaternary ammonium salt **4** in a 79% yield. For the
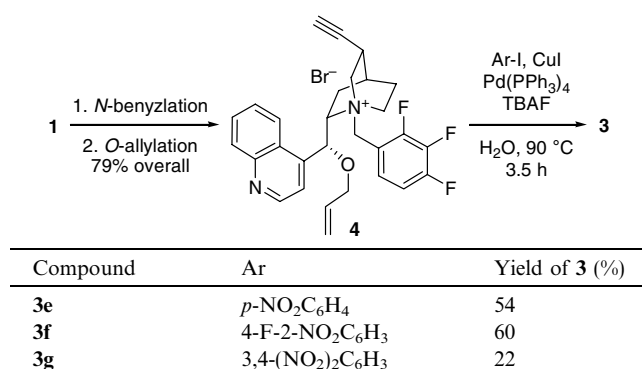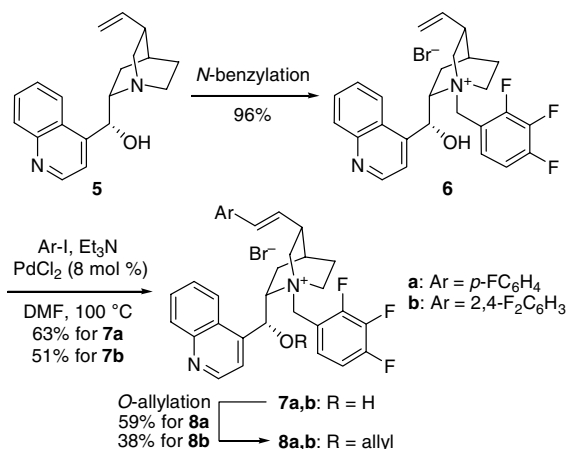
coupling of **4** with nitroaryl iodides, we found that the highest yields were obtained by employing TBAF as base[11] under aqueous conditions. We were unable to obtain 3,4-dinitrophenyl-substituted salt **3g** in good yield; nevertheless, enough of this compound was produced to examine its viability as a catalyst in the asymmetric aldol reaction.

C3-Alkenyl-substituted chiral ammonium salts **8** bearing fluorinated aryl groups were assembled as illustrated in Scheme 2, with a Heck reaction as the key step. Performing the Heck reaction after the N-benzylation and before the O-allylation delivered optimal results. The previously developed conditions were satisfactory for the benzylation and allylation steps, and PdCl$_2$/Et$_3$N was found to be the best system for the Heck coupling of ammonium salt **6** with fluorinated aryl iodides.

In addition to the catalysts bearing electron-deficient groups at C3, we were interested in constructing dimeric catalysts linked through a C3 alkyne. Although dimeric cinchonidine-derived chiral phase-transfer catalysts are known, all previous examples of which we are aware involve dimerization via an *N*-benzyl or *N*-alkyl group.[12] Thus, we decided to prepare a novel class of dimeric chiral ammonium salt catalysts. The synthesis of these catalysts is shown in Scheme 3. The previously constructed alkyne **4** could be dimerized in an Eglinton coupling,[13] affording diyne **9** in good yield. We initially attempted to prepare phenyl-linked dimer **10a** and biphenyl-linked dimer **10b** in a single Sonogashira coupling employing 2 equiv of **4** and the appropriate aryl di-iodide. However, this approach was unsuccessful, so we performed two sequential couplings instead. The second reaction required increased loadings of the palladium and copper catalysts, and the products were obtained in modest yields. Each of the bis-ammonium salts **9** and **10** was extremely polar, requiring pure CH$_3$OH for elution from a silica gel column.

Catalysts **3a–g**, **8a–b**, **9**, and **10a–b** were evaluated in the aldol reaction between hydrocinnamaldehyde (**11**) and *tert*-butyl glycinate benzophenone imine (**12**). The results of this investigation are contained in Table 3. For purposes of comparison, the Park–Jew catalyst mediates

Table 2. Synthesis of C3-alkynyl ammonium salts **3e–g**

Compound	Ar	Yield of **3** (%)
3e	*p*-NO$_2$C$_6$H$_4$	54
3f	4-F-2-NO$_2$C$_6$H$_3$	60
3g	3,4-(NO$_2$)$_2$C$_6$H$_3$	22

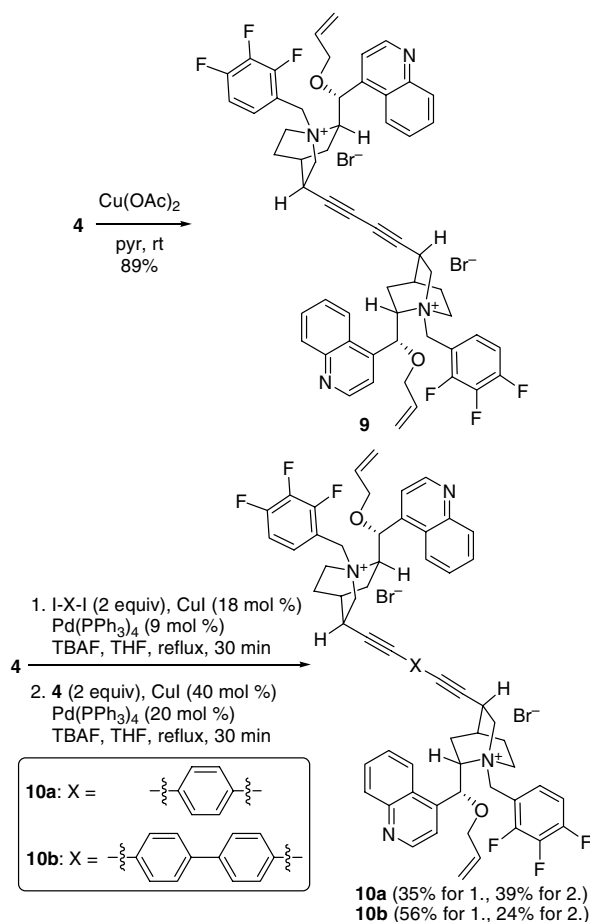**Scheme 2.** Synthesis of C3-alkenyl ammonium salts **8a** and **8b**.

Scheme 3. Synthesis of dimeric ammonium salts **9** and **10**.

Table 3. Survey of catalysts in asymmetric aldol reaction

Catalyst	Yield (%)	*syn/anti*	*syn* ee[b] (%)	*anti* ee[b] (%)
3a	86	1.2:1	82	39
3b	54	2.6:1	82	36
3c	40	1.5:1	79	30
3d	50	1:1.8	91	44
3e	76	1.3:1	83	34
3f	57	1:4.7	20	5
3f[a]	40	1:1.1	61	8
3g	76	1:3.7	13	3
3g[a]	50	1:2.2	25	9
8a	38	1:1.5	51	3
8b	38	1.1:1	65	14
9[a]	57	1:1.3	43	2
10a[a]	57	1.1:1	85	38
10b[a]	50	1:1.2	74	23

[a] CH$_2$Cl$_2$ was used as the solvent.
[b] Measured by HPLC (Chiralcel OD–H, 98:2 hexanes–*i*-PrOH, 1 mL/ min).

the reaction between **11** and **12** to afford a 64% yield of **13** with a *syn/anti* ratio of 1.3:1. The *syn* and *anti* iso-

mers are obtained with 80% and 33% ee, respectively.[5] Ammonium salt **3d** possessing a 2,4-difluorophenyl-substituted alkyne afforded the best ee's of any of our new catalysts; unfortunately, the diastereoselectivity was both modest and reversed, with the major *anti* isomer having low ee. In fact, *anti*-**13** was produced in low ee by all of the catalysts examined. *p*-Fluorophenyl-substituted alkyne catalyst **3b** was able to improve the diastereoselectivity of the reaction (2.6:1 dr in favor of the *syn* isomer), but no enhancement of ee's was observed. Comparison of the results obtained with **3b** and **3d** shows that the presence or absence of an *ortho* fluoro substituent exerts a significant effect on the aldol reaction. While the underlying reasons for this effect are unclear, it is possible that aromatic F ··· H interactions[14] could be involved. Catalyst **3a**, which bears a *p*-trifluoromethyl-substituted phenyl group on the alkyne, afforded the aldol products in very good yield (86%); however, the dr and ee's were similar to those delivered by the Park–Jew catalyst. *Z*-Alkene-containing catalysts **8a** and **8b** performed more poorly than did their alkyne analogues **3b** and **3d**, indicating that the geometry of the C3-substituent plays an important role in catalyst efficiency.

Dimeric catalysts **9** and **10a–b** were insoluble in the toluene–chloroform solvent system used for most of the aldol reactions.[15] Thus, reactions employing these compounds were performed in CH$_2$Cl$_2$. Inspection of the results obtained with the dimers reveals that the phenyl group serves as the optimal spacer between the two catalyst units (cf. **10a** vs **9** and **10b**). Nevertheless, none of the dimeric ammonium salts performed better than the Park–Jew catalyst in the aldol reaction.

In conclusion, we have synthesized novel monomeric and dimeric cinchonidine-derived chiral ammonium salts and examined their efficiency in the construction of β-hydroxy α-amino acids via asymmetric aldol reactions.[16] We have discovered individual catalysts which improve upon the performance of the Park–Jew catalyst in terms of yield (**3a**), *syn/anti* ratio (**3b**), and ee (**3d**). We have yet to find a single catalyst which performs well in all three areas. Currently, the biggest limitation of this method is the modest diastereoselectivity. Since asymmetric alkylations of **12** mediated by cinchonidine-derived phase-transfer catalysts typically proceed with excellent ee, the problem is likely due to low facial selectivity of the aldehyde. The methods developed in this study for functionalization of the *Cinchona* alkaloid scaffold (Sonogashira coupling, Heck reaction) should prove useful to others interested in modifying this class of alkaloids.

Supplementary data

Experimental procedures and characterization data for compounds **3** and **8**–**10** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.132.

References and notes

1. (a) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266; (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; (d) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961.
2. Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367.
3. For an effective BINOL-based phase-transfer catalyst, see: (a) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685; (b) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542. However, the high cost of BINOL and the lengthy synthesis required for this catalyst makes the development of cinchonidine-derived catalysts accessible via short routes a worthy goal.
4. Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I.-Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.
5. Mettath, S.; Srikanth, G. S. C.; Dangerfield, B. S.; Castle, S. L. *J. Org. Chem.* **2004**, *69*, 6489.
6. (a) Braje, W. M.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Beil, W.; Hoffmann, H. M. R. *Helv. Chim. Acta* **2000**, *83*, 777; (b) Frackenpohl, J.; Braje, W. M.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 47.
7. Lambers, M.; Beijer, F. H.; Padron, J. M.; Toth, I.; de Vries, J. G. *J. Org. Chem.* **2002**, *67*, 5022.
8. Merschaert, A.; Delbeke, P.; Daloze, D.; Dive, G. *Tetrahedron Lett.* **2004**, *45*, 4697.
9. Hoffman, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293.
10. Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733.
11. Liang, Y.; Xie, Y.-X.; Li, J.-H. *J. Org. Chem.* **2006**, *71*, 379.
12. (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927; (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036; (c) Siva, A.; Murugan, E. *J. Mol. Catal. A: Chem.* **2005**, *241*, 111.
13. Tobe, Y.; Utsumi, N.; Nagano, A.; Sonoda, M.; Naemura, K. *Tetrahedron* **2001**, *57*, 8075.
14. Doyon, J. B.; Jain, A. *Org. Lett.* **1999**, *1*, 183.
15. For the original application of this solvent mixture in phase-transfer-catalyzed alkylations, see Refs. 4,12b.
16. For recent developments in the synthesis of β-hydroxy α-amino acids, see: (a) Makino, K.; Iwasaki, M.; Hamada, Y. *Org. Lett.* **2006**, *8*, 4573; (b) Crich, D.; Banerjee, A. *J. Org. Chem.* **2006**, *71*, 7106. Please see the latter paper or Ref. 5 for a summary of the strategies employed in the asymmetric synthesis of these compounds.