ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 10632–10634

www.rsc.org/chemcomm

COMMUNICATION

Optically pure bulky (hetero)arylalkyl carbinols *via* kinetic resolution†

Bin Hu,[a] Meng Meng,[a] John S. Fossey,[ab] Weimin Mo,[c] Xinquan Hu[c] and Wei-Ping Deng*[a]

Received 27th July 2011, Accepted 18th August 2011
DOI: 10.1039/c1cc14591f

Planar chiral nucleophilic catalyst Fc-PIP was employed in the kinetic resolution of bulky (hetero)arylalkyl carbinols delivering unreacted alcohols with extremely high enantiomeric excess (>99.0% ees) in ideal conversions ranging from 50.4–56.7%.

Chiral bulky (hetero)arylalkyl carbinols are versatile synthetic building blocks that can be found in biologically active units,[1] in the synthesis of natural products and their analogs,[2] as chiral auxiliaries[3] and as chiral ligands.[4] Bulky alcohol **1** can be converted into useful chiral bipyridine ligand **2** (Fig. 1),[4a,f] which has been employed in catalytic asymmetric transformations,[4a–f,5] including the asymmetric ring-opening of *meso*-epoxides,[5d,e] asymmetric Michael additions.[5c,f] 9-Anthryl-*tert*-butyl carbinol **3** has been used as a chiral auxiliary[3] and has been incorporated into a dihydroxylation catalyst by Corey and Zhang.[4g]

The synthesis of such bulky (hetero)arylalkyl carbinols often relies upon oxidative kinetic resolution[6] or asymmetric reduction protocols.[4a,d,g] Noyori and coworkers reported that asymmetric hydrogenation of *tert*-alkyl ketones using homogeneous chiral $RuCl_2$[(*S*)-tolbinap](pica) complexes delivered bulky arylalkyl carbinols in excellent yields and enantioselectivities (up to 98% ee),[7a] although heteroaryl substrates were not quite so well tolerated, presumably due to the deactivation of catalyst by potential coordination of heteroatoms to the ruthenium catalyst.[7b] Subsequently ruthenium complexes bearing chiral tridenate ligands were developed by Clarke *et al.* for the enantioselective reduction of bulky ketones either by hydrogenation or hydrogen transfer, affording the corresponding chiral carbinols in moderate ee.[8] As such the development of new methods capable of delivering heteroarylalkyl carbinols in high ee continues to be an important challenge in synthetic chemistry.

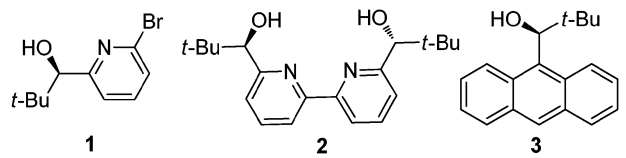


Fig. 1 Bulky (hetero)arylalkyl carbinols.

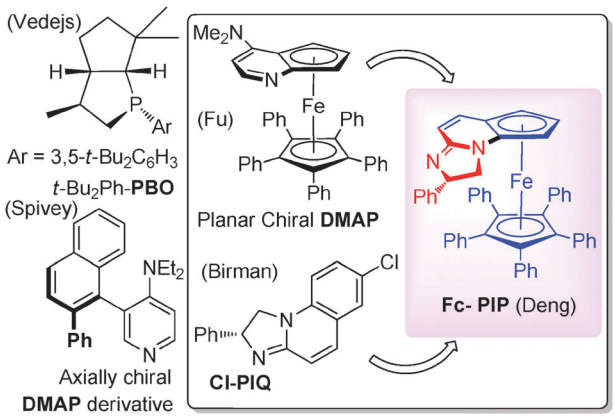


Fig. 2 Representative nonenzymatic nucleophilic catalysts.

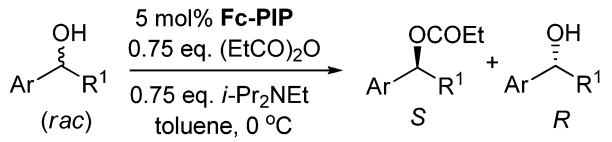
Catalytic kinetic resolution (KR) of secondary alcohols through acyl transfer using nonenzymatic nucleophilic catalysts is one of the effective approaches for the generation of chiral alcohols.[9–14] Over the past two decades, significant progress has been made in the development of new families of chiral nonenzymatic acylation catalysts, including chiral phosphines,[10] 2,3-dihydroimidazo derivatives[11] and 4-(dimethylamino) pyridine (DMAP) equivalents with central,[12] axial,[13] helical[14] and planar chirality (Fig. 2).[15] Whilst such catalysts were effective for the kinetic resolution of a range of secondary alcohols, it is notable that catalysts for the acylative KR of heteroarylalkyl carbinols have, to the best of our knowledge, not yet been reported.

Our own planar chiral ferrocene derivative (**Fc-PIP**) for nucleophilic catalysis (Fig. 2),[16,17] that combines two inspirational catalyst systems of Fu *et al.*[15] and Birman *et al.*[11] into a hybrid chiral nucleophilic catalyst, showed extraordinary selectivity factors *S* of up to 1892 in the kinetic resolution of phenyl *tert*-butyl carbinol.[16] In light of our good results we turned our attention to the kinetic resolution of bulky secondary alcohols including heteroarylalkyl carbinols. Therefore, a series of chiral racemic bulky (hetero)arylalkyl carbinols **1**, **3–15** were prepared and subjected to our developed catalytic KR system (Scheme 1).

In our previous study, phenyl *tert*-butyl carbinol **4** underwent catalytic KR using 2 mol% of **Fc-PIP** in toluene at 0 °C to

[a] *Shanghai Key Laboratory of Functional Materials Chemistry, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China. E-mail: weiping_deng@ecust.edu.cn*
[b] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. E-mail: j.s.fossey@bham.ac.uk*
[c] *College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China. E-mail: mowm@zjut.edu.cn*

† Electronic supplementary information (ESI) available: CIF file for (R,R_P)-Fc-PIP and general experimental procedure, HPLC data analysis for all kinetic resolution of *rac*-alcohols. CCDC 837133. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14591f



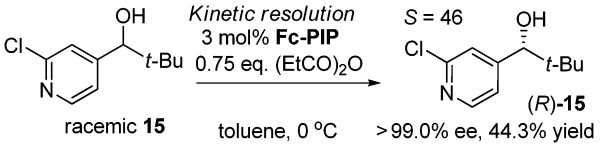
Scheme 1 Kinetic resolution of bulky arylalkyl carbinols using **Fc-PIP**.

give the corresponding ester and unreacted alcohol in >99.0% ee and 81.1% ee, respectively, with a selectivity factor S = 534 at 45% conversion, notably the low reactivity of these substrates meant 50% conversion was not readily accomplished, even with a prolonged time of 24 h.

Herein an increase of catalyst loading to 5 mol% improved the conversion (48.5% at 11 h) to give the corresponding ester and unreacted alcohol in >99.0% and 93.2% ees, with an improved S value of 690 (Table 1, entry 1). As expected, the percentage recovery and the ee of unreacted alcohol was improved to 50.4% and >99.0%, respectively, accompanied by a slightly reduced ee of ester due to the slight over-acylation (98.2% ee, S = 683) when a longer reaction time was used, 24 h (Table 1, entry 2). Next the bulky carbinols **3–15** were exposed to the newly optimised reaction conditions. Surprisingly aryl *tert*-butyl carbinols **5** and **6**, with substituents in the *para* position, suffered from reduced S values affording unreacted alcohols in 98.0% and 96.0% ees respectively (Table 1, entries 3 and 4, S = 118 for **5** and 61 for **6**). Next a variety of bulky secondary alcohols including aryl-*tert*-butyl alcohols with extended aromatic systems (**3**, **7–8**), phenyl-*tert*-butyl gem dimethyl derivatives (**9–11**), and heteroaryl-*tert*-butyl carbinols (**1**, **12–15**) were investigated under optimal reaction conditions. Catalyst **Fc-PIP** worked well to afford the corresponding unreacted alcohols in extraordinarily high enantiomeric excess (>99.0%) and in good to excellent yields (43–48%) (Table 1, entries 7–17). 9-Anthryl-*tert*-butyl carbinol **3** was resolved very slow with only a moderate selectivity factor S = 37 (Table 1, entry 9, >99.0% ee, 4 days). Synthetically useful bulky alcohols **9–11**[18] underwent catalytic KR reactions with selectivity factors S ranging from 68 to 86 delivering the corresponding unreacted alcohols in >99.0% ees with recovery >45% (Table 1, entries 10–12).

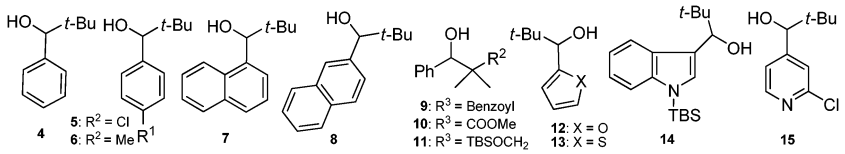
Heteroaryl-*tert*-butyl carbinols (**1**, **12–15**), which have not yet been studied in nonenzymatic acyl transfer catalysis, worked well in the catalytic KR reaction with **Fc-PIP** and allowed isolation of the corresponding unreacted alcohols in >99.0% ees (Table 1, entries 13–17, S value ranging from 37–74). Among them, 6-(2-bromopyridinyl)-*tert*-butyl alcohol **1** and TBS protected 3-indolyl-*tert*-butyl **14** were relatively inert, and either 15 mol% of catalyst loading or increased temperatures (room temperature) were necessary to achieve acceptable resolution results (Table 1, entries 15–16). Interestingly, relatively electron-deficient 4-(2-chloro-pyridinyl)-*tert*-butyl alcohol **15** was much more reactive than **1** with a higher S value (74 *versus* 39). By contrast catalytic KR of **15** using Birman's **Cl-PIQ** catalyst gave a selectivity factor S = 13 after 48 h (Table 1, entry 18).

To further demonstrate the utility of this process, a reasonable scale (800 mg) catalytic KR of bulky alcohol **15** was performed,[19] using 3 mol% of **Fc-PIP** as a catalyst. This reaction



Scheme 2 Larger scale catalytic KR of racemic **15**.

Table 1 Kinetic resolution of bulky (hetro)arylalkyl carbinols using **Fc-PIP**



Entry	Substrate	t/h	ee_E[a] (%)	ee_A[b] (%)	C_{HPLC}[c] (%)	S[c]
1	**4**	11	**>99.0**	93.2	48.5	690
2	**4**	24	98.2	**>99.0**	50.4	683
3	**5**	7	92.5	98.0	51.4	118
4	**6**	10.5	88.0	96.0	52.2	61
5	**5**	11	91.6	**>99.0**	51.9	120
6	**6**	93	79.8	**>99.0**	55.6	59
7	**7**	48	85.2	**>99.0**	53.8	71
8	**8**	19	92.6	**>99.0**	51.7	142
9	**3**	96	75.8	**>99.0**	56.6	37
10	**9**	93	83.8	**>99.0**	54.3	68
11	**10**	36	85.4	**>99.0**	53.9	85
12	**11**	93	88.6	**>99.0**	52.8	86
13	**12**	93	80.6	**>99.0**	55.1	48
14	**13**	48	86.2	**>99.0**	53.5	73
15	**1**[d]	78	76.8	**>99.0**	56.3	39
16	**14**[e]	72	75.6	**>99.0**	56.7	37
17	**15**	15.5	86.8	**>99.0**	53.7	74
18	**15**[f]	48	53.6	97.6	64.6	13

[a] The ee of the ester product. [b] The ee of the unreacted alcohol, which was tested at least three times for the ees >99.0%. [c] Calculated from the ee of the ester and unreacted alcohol. [d] Using 15 mol% of catalyst **Fc-PIP**. [e] Room temperature. [f] Using 5 mol% of catalyst **Cl-PIQ**.

proceeded smoothly to afford unreacted alcohol **15** in >99.0% ee with good selectivity factor $S = 46$ and in 44.3% yield (Scheme 2). After routine work-up the catalyst was readily recovered (95%).

In summary, we have demonstrated that planar-chiral **Fc-PIP** can catalyse the acyl transfer kinetic resolution of a wide range of bulky alcohols with remarkable efficiency, affording unreacted alcohols in extremely high enantiomeric excess (>99.0%) and in good yields (43.3–49.6%; ideal conversion 50%). Importantly a practical method for accessing a range of bulky carbinols, including synthetically important heteroaryl carbinols in excellent ees (>99.0%), was demonstrated.

WPD thanks the "Shu Guang" project of Shanghai Education Development Foundation (No. 09SG28); JSF and WPD thank the NSFC (No. 21050110426 and 21172068) and Catalysis and Sensing for our Environment network. JSF thanks ECUST, the University of Birmingham and ERDF AWM II; WMM thanks the NSFC (No. 20876149)

Notes and references

1 (*a*) J. Singh, J. Thurmond, M. E. R. Butchbach, M. Haraldsson and B. Pease, *J. Med. Chem.*, 2008, **51**, 449–469; (*b*) P. V. Ramachandran, J. S. Chandra, B. Prabhudas and D. Pratihar, *Org. Biomol. Chem.*, 2005, **3**, 3812–3824; (*c*) X. Hu and R. M. Kellogg, *Synthesis*, 1995, 533–538.

2 (*a*) M. G. Moloney, C. L. Bagwell and A. L. Thompson, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4081–4086; (*b*) M. G. Moloney, C. L. Bagwell and M. Yaqoob, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2090–2094; (*c*) F. Richter, C. Maichle-Mössmer and M. E. Maier, *Synlett*, 2002, 1097–1100.

3 (*a*) A. Virgili and A. Carriere, *Tetrahedron: Asymmetry*, 1996, **7**, 227–230; (*b*) A. Carriere, A. Virgili and M. Figueredo, *Tetrahedron: Asymmetry*, 1996, **7**, 2793–2796.

4 (*a*) C. Bolm, M. Zehnder and D. Bur, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 205–207; (*b*) G. Chelucci and F. Soccolini, *Tetrahedron: Asymmetry*, 1992, **3**, 1235–1238; (*c*) C. Bolm, N. Derrien and A. Seger, *Synlett*, 1996, 387–388; (*d*) H. C. Brown, G.-M. Chen and P. V. Ramachandran, *Chirality*, 1997, **9**, 506–511; (*e*) C. Bolm, C. L. Dinter, A. Seger and H. Hocher, *J. Org. Chem.*, 1999, **64**, 5730–5731; (*f*) S. Kobayashi, S. Ishikawa, T. Hamada and K. Manabe, *Synthesis*, 2005, 2176–2182; (*g*) E. J. Corey and J.-H. Zhang, *Org. Lett.*, 2001, **3**, 3211–3214; (*h*) A. C. Dros, A. Meetsma and R. M. Kellogg, *Tetrahedron*, 1999, **55**, 3071–3090.

5 (*a*) C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169–1190; (*b*) C. Bolm, G. Schlingloff and K. Harms, *Chem. Ber.*, 1992, **125**, 1191–1203; (*c*) C. Bolm, M. Zehnder and D. Bur, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 205–207; (*d*) C. Bolm and M. Ewald, *Tetrahedron Lett.*, 1990, **31**, 5011–5012; (*e*) C. Schneider, M. V. Nandakumar and S. Ghosh, *Eur. J. Org. Chem.*, 2009, 6393–6398; (*f*) S. Kobayashi, M. Boudou and C. Ogawa, *Adv. Synth. Catal.*, 2006, **348**, 2585–2589; (*g*) E. Mai and C. Schneider, *Chem.–Eur. J.*, 2007, **13**, 2729–2741; (*h*) S. Kobayashi, M. Ueno, T. Kitanosono and M. Sakai, *Org. Biomol. Chem.*, 2011, **9**, 3619–3621; (*i*) H.-L. Kwong, W.-S. Lee, C.-T. Yeung, K.-C. Sham and W.-T. Wong, *Polyhedron*, 2011, **30**, 178–186.

6 (*a*) F. Sato, Y. Kobayashi, M. Kusakabe and Y. Kitano, *J. Org. Chem.*, 1988, **53**, 1586–1587; (*b*) F. Sato, M. Kusakabe, Y. Kitano and Y. Kobayashi, *J. Org. Chem.*, 1989, **54**, 2085–2091; (*c*) F. Sato, Y. Kitano, M. Kusakabe and Y. Kobayashi, *J. Org. Chem.*, 1989, **54**, 994–996.

7 (*a*) R. Noyori, T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q.-H. Lin and Y.-M. Wei, *J. Am. Chem. Soc.*, 2005, **127**, 8288–8289; (*b*) I. C. Lennon and J. A. Ramsden, *Org. Process Res. Dev.*, 2005, **9**, 110–112.

8 (*a*) M. L. Clarke, M. B. D. Valenzuela and A. M. Z. Slawin, *Organometallics*, 2007, **26**, 16–19; (*b*) M. L. Clarke, M. B. D. Valenzuela, S. D. Phillips, M. B. France and M. E. Gunn, *Chem.–Eur. J.*, 2009, **15**, 1227–1232; (*c*) M. L. Clarke, S. D. Phillips and J. A. Fuentes, *Chem.–Eur. J.*, 2010, **16**, 8002–8005.

9 For reviews: (*a*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974–4001; (*b*) A. C. Spivey and S. Arseniyadis, *Top. Curr. Chem.*, 2010, **291**, 233–280; (*c*) C. E. Müller and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2011, **50**, 6012–6042.

10 (*a*) E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430–431; (*b*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 1999, **121**, 5813–5814; (*c*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 2003, **125**, 4166–4173; (*d*) E. Vedejs and J. A. Mackay, *J. Org. Chem.*, 2006, **71**, 498–503.

11 (*a*) V. B. Birman, E. W. Uffman, H. Jiang, X.-M. Li and C. J. Kilbane, *J. Am. Chem. Soc.*, 2004, **126**, 12226–12227; (*b*) V. B. Birman and H. Jiang, *Org. Lett.*, 2005, **7**, 3445–3447; (*c*) V. B. Birman, X.-M. Li, P. Liu and K. N. Houk, *J. Am. Chem. Soc.*, 2008, **130**, 13836–13837; (*d*) V. B. Birman and Y.-H. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2525–2529.

12 (*a*) S. Yamada, T. Misono, Y. Iwai and A. Masumizu, *J. Org. Chem.*, 2006, **71**, 6872–6880; (*b*) S. Yamada and K. Yamashita, *Tetrahedron Lett.*, 2008, **49**, 32–35; (*c*) K. Fuji, T. Kawabata, M. Nagato and K. Takasu, *J. Am. Chem. Soc.*, 1997, **119**, 3169–3170; (*d*) T. Fuji, T. Kawabata, R. Stragies and T. Fukaya, *Chirality*, 2003, **15**, 71–76; (*e*) E. Vedejs and X.-H. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809–1810; (*f*) E. Vedejs, T. A. Duffey and J. A. Mackay, *J. Org. Chem.*, 2010, **75**, 4674–4685; (*g*) E. Vedejs, S. A. Shaw and P. Aleman, *J. Am. Chem. Soc.*, 2003, **125**, 13368–13369; (*h*) E. Vedejs, T. A. Duffey and S. A. Shaw, *J. Am. Chem. Soc.*, 2009, **131**, 14–15; (*i*) I. B. Campbell, G. Priem, B. Pelotier and S. J. F. Macdonald, *J. Org. Chem.*, 2003, **68**, 3844–3848; (*j*) D. Diez, M. J. Gil, R. F. Moro and N. M. Garrido, *Tetrahedron: Asymmetry*, 2005, **16**, 2980–2985; (*k*) S. J. Connon, C. O. Dalaigh, S. J. Hynes and D. J. Maher, *Org. Biomol. Chem.*, 2005, **3**, 981–984; (*l*) S. J. Connon, C. O. Dalaigh and S. J. Hynes, *Org. Biomol. Chem.*, 2006, **4**, 2785–2793.

13 (*a*) A. C. Spivey, F.-J. Zhu, M. B. Mitchell and S. G. Davey, *J. Org. Chem.*, 2003, **68**, 7379–7385; (*b*) A. C. Spivey, S. Arseniyadis, T. Fekner, A. Maddaford and D. P. Leese, *Tetrahedron*, 2006, **62**, 295–301.

14 D. R. Carbery, M. R. Crittall and H. S. Rzepa, *Org. Lett.*, 2011, **13**, 1250–1253.

15 (*a*) G. C. Fu, J. C. Ruble and H. A. Latham, *J. Am. Chem. Soc.*, 1997, **119**, 1492–1493; (*b*) G. C. Fu, B. Tao, J. C. Ruble and D. A. Hoic, *J. Am. Chem. Soc.*, 1999, **121**, 5091–5092; (*c*) M. Johannsen, J. G. Seitzberg, C. Dissing and I. Sotofte, *J. Org. Chem.*, 2005, **70**, 8332–8337; (*d*) S. Yamada and J. S. Fossey, *Org. Biomol. Chem.*, 2011, **9**, DOI: 10.1039/c1ob05228d.

16 B. Hu, M. Meng, Z. Wang, W. Du, J. S. Fossey, X. Hu and W.-P. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 17041–17044.

17 The new X-ray crystal structure of (S, R_p) **Fc-PIP** is given in the ESI† of this report, thus obtained corroborating earlier assertions (ref. 16) of the structural influences in catalysis.

18 (*a*) S. Kobayashi, H. Ishitani, Y. Yamashita and H. Shimizu, *J. Am. Chem. Soc.*, 2000, **122**, 5403–5404; (*b*) S. Kobayashi, Y. Yamashita, H. Ishitani and H. Shimizu, *J. Am. Chem. Soc.*, 2002, **124**, 3293–3302; (*c*) S. E. Denmark, G. L. Beutner, T. Wynn and M. D. Eastgate, *J. Am. Chem. Soc.*, 2005, **127**, 3774–3789; (*d*) K. A. Jorgensen, W. Zhuang and T. B. Poulsen, *Org. Biomol. Chem.*, 2005, **3**, 3284–3289; (*e*) S. Kobayashi, K. Seki and M. Ueno, *Org. Biomol. Chem.*, 2007, **5**, 1347–1350; (*f*) S. L. Wiskur and S. G. Patel, *Tetrahedron Lett.*, 2009, **50**, 1164–1166; (*g*) M. Nakajima, S. Kotani, Y. Shimoda, T. Tando and M. Sugiura, *Tetrahedron: Asymmetry*, 2009, **20**, 1369.

19 Y. Fort, S. Choppin and P. Gros, *Eur. J. Org. Chem.*, 2001, 603–606.

