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Chiral isoxazolidine-mediated stereoselective umpolung α-phenylation of methyl ketones†

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An effective asymmetric α-phenylation of methyl ketones with triphenylaluminium in the presence of (+)-benzopyranoisoxazolidine has been developed. The reaction proceeds *via* the *in situ* formation of a chiral *N*-alkoxyenamine and the subsequent diastereoselective nucleophilic phenylation to provide α-phenylated products in moderate to good yields, with high enantioselectivities.

Enantioenriched acyclic α-aryl carbonyl compounds are versatile intermediates for the synthesis of biologically active molecules and pharmaceutical agents, including the nonsteroidal anti-inflammatory drug (NSAID) naproxen,[1] antiplatelet agent clopidogrel,[2] and central nervous system stimulant dexmethylphenidate.[3] Therefore, a variety of methodologies have been developed for the asymmetric synthesis of enolizable α-aryl carbonyl compounds. The nickel-catalysed asymmetric cross-coupling of α-bromoketones with aryl magnesium[4a] and aryl zinc reagents[4b] and the nickel-catalysed reductive acyl cross-coupling of acyl chlorides with secondary alkyl halides[5] are particularly reliable methods for the synthesis of enantioenriched acyclic α-aryl ketones. A few other methods[6] have also been developed for this purpose, but they often involve additional steps for the preparation of the starting materials. Therefore, a straightforward synthetic route to enantioenriched acyclic α-aryl ketones from readily available and simple ketones is desirable.

Umpolung of the α-carbon atom in carbonyl compounds is an attractive reaction because it allows the direct introduction of various substituents into the α-position using a nucleophile.[7–9] However, the asymmetric nucleophilic introduction into the α-position of ketones and their equivalents is scarce.[10] To the best of our knowledge, the asymmetric introduction of a carbon nucleophile into the α-position of ketones is limited to the umpolung α-alkylation of β-ketoimides bearing an Evans' oxazolidinone as a chiral auxiliary using Koser's reagent (PhI(OH)OTs) and dialkylzinc reagents.[11] This method involves separate steps for the introduction and removal of the chiral auxiliary, to furnish the desired enantioenriched ketone. Therefore, highly effective asymmetric introduction into the α-position of ketones by an umpolung strategy remains a frontier area of research in synthetic organic chemistry. In this communication, we report the asymmetric α-phenylation of ketones **1** with triphenylaluminium in the presence of (+)-benzopyranoisoxazolidine **3**[12] for the preparation of enantioenriched α-phenyl ketones **2** (Scheme 1). Owing to their simplicity, convenience, and high enantioselectivity, asymmetric umpolung α-phenylation of simple ketones is a straightforward synthetic route to enantioenriched acyclic α-phenyl ketones. This protocol is advantageous in that no additional procedure for the introduction and removal of the chiral isoxazolidine is required.

To accomplish the asymmetric nucleophilic α-phenylation of ketones, we first optimized the conditions for the umpolung α-phenylation of ketone **1a** (Table 1). The reaction of **1a** with triphenylaluminium (2 equiv.) in the presence of (+)-benzopyranoisoxazolidine **3** (2 equiv.) at 0 °C gave α-phenylated ketone **2a** in moderate yield with high enantioselectivity (entry 1). The absolute configuration of **2a** could be determined as (*R*) because the optical rotation sign of **2a** and that of the one reported in the literature are negative.[13] Pleasingly, an increase in the amount of

Scheme 1 Asymmetric introduction of a nucleophile into the α-position of ketones through an umpolung process.

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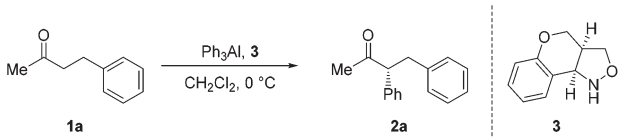
Table 1 Optimization of conditions for the asymmetric nucleophilic α-phenylation of **2a**



1a **2a** **3**

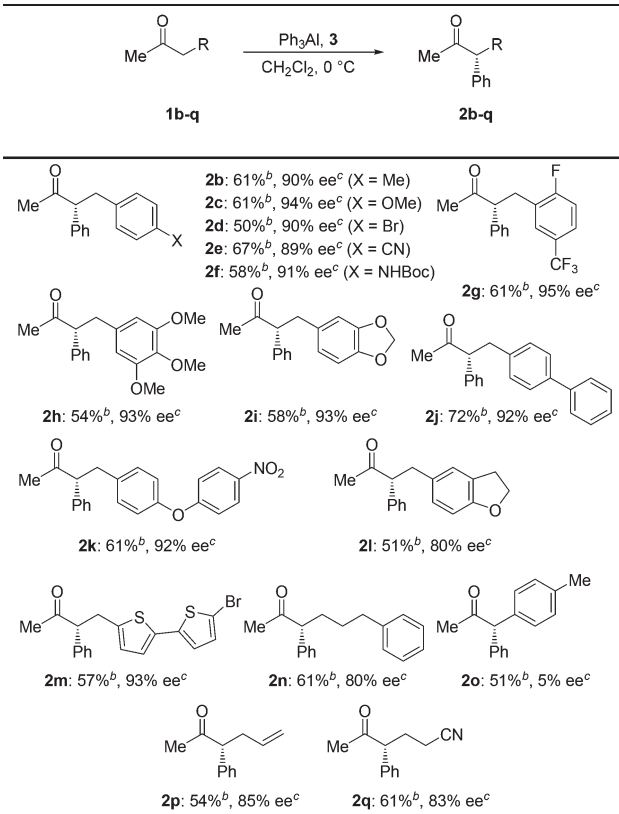
Entry	Ph_3Al (eq.)	**3** (eq.)	Yield[a] (%)	ee[b] (%)
1	2	2	58	94
2	3	2	66	94
3	3	1	51	93
4	1	2	14	85

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase.

triphenylaluminium (3 equiv.) improved the yield of **2a** while ensuring high enantioselectivity (entry 2). In contrast, a significant decrease in the yield was observed when the amount of triphenylaluminium was reduced to 1 equiv. (entry 4).[14]

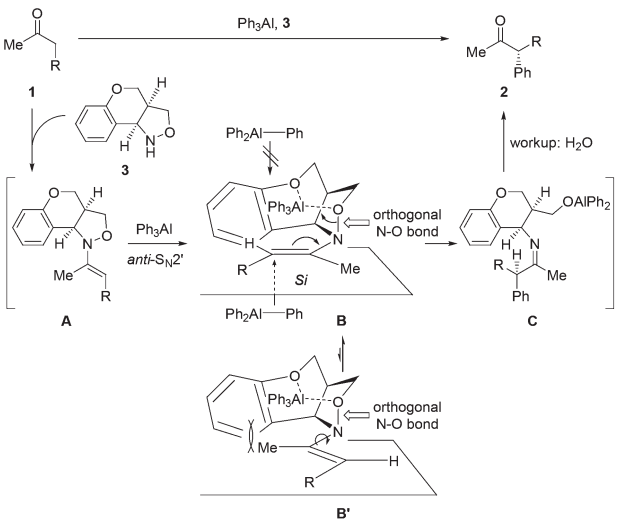
With the optimized reaction conditions in hand (Table 1, entry 2), we next examined the substrate scope of the asymmetric umpolung reaction (Table 2). The asymmetric phenylation of **1b–f** with *p*-methyl, *p*-methoxy, *p*-bromo, *p*-cyano, and Boc-protected *p*-amino groups on the benzene ring proceeded smoothly at 0 °C to give the desired products **2b–f** with high enantioselectivities. Moreover, various functional groups (fluoro, trifluoromethyl, methylenedioxy, phenyl, and aryloxy groups) and heterocycles (dihydrobenzofuran and thiophene) were well tolerated in the asymmetric phenylation (**2g–m**). The asymmetric α-phenylation of **1n** successfully afforded **2n** with good enantioselectivity. However, the reaction of **1o**, which is one-carbon dehomologated as compared to **1a**, gave α-phenylated ketone **2o** with low enantioselectivity, possibly because the α-stereocenter of **5o** was easily racemized under the reaction conditions. Aliphatic methyl ketones **1p** and **1q** were also used in this reaction, and the corresponding α-phenylated ketones **2p** and **2q** were obtained in moderate yields with good enantioselectivities.[15–17]

Table 2 Substrate scope[a]

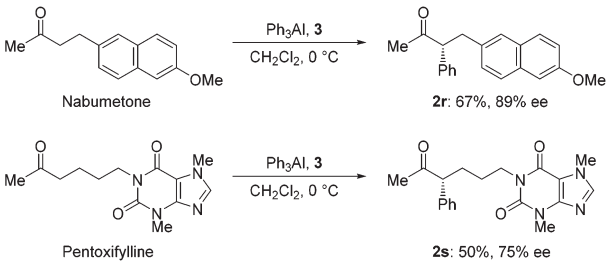


[a] Reaction conditions: **1** (0.075 mmol), **3** (0.15 mmol), and Ph_3Al (0.23 mmol) in CH_2Cl_2 at 0 °C for 2–3 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

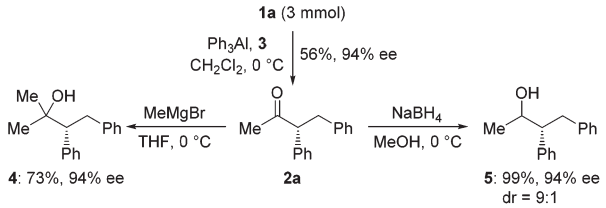
A plausible reaction pathway for the formation of enantioenriched (*R*)-α-phenyl ketone **2** is depicted in Scheme 2. This umpolung reaction includes (i) the generation of *N*-alkoxyenamine **A**; (ii) coordination with a nucleophilic aluminium reagent (**A** → **B**); (iii) N–O bond cleavage and a simultaneous nucleophilic attack of the nucleophilic aluminium reagent (**B** → **C**); and (iv) the hydrolysis of the imine intermediate **C**. The stereochemical feature of this reaction can be rationalized as follows. First, the thermodynamically stable (*E*)-*N*-alkoxyenamine **A** would be formed by the condensation of ketone **1** and chiral isoxazolidine **3**. When chiral enamine **A** reacts with triphenylaluminium, two conformations **B** and **B′** can be considered. The σ* (N–O bond cleavage) and π* orbitals (enamine moiety) are aligned in both conformations. Conformation **B** should be favoured over **B′** due to the steric repulsion between the methyl group and the benzene ring. Therefore, a nucleophilic attack by another triphenylaluminium onto the *Si* (bottom) face is favoured by the *anti*-S_N2' displacement, presumably because of the steric inter-



Scheme 2 The proposed reaction pathway and stereochemical feature of asymmetric umpolung phenylation to *N*-alkoxyenamine.



Scheme 3 Asymmetric α-phenylation of biologically active ketones.



Scheme 4 Scalable synthesis and synthetic modification of **2a**.

actions with the triphenylaluminium moiety coordinated with the oxygen atoms of the two ethers in the chiral auxiliary.

We next examined the asymmetric α-phenylation of biologically active compounds. The nonacidic NSAID nabumetone and the phosphodiesterase inhibitor pentoxifylline were selected for our asymmetric umpolung reaction (Scheme 3). The asymmetric introduction of a phenyl group into these compounds was successfully achieved to obtain the corresponding α-phenylated ketones **2r** and **2s** in moderate yields, with moderate to good enantioselectivities. Therefore, our protocol can provide an expedient approach to enantioenriched α-phenylmethyl ketones.

It is worth mentioning that the scalable synthesis of α-phenyl ketone **2a** was performed under optimized conditions, and the desired **2a** was obtained in 56% yield with 94% ee when the amount of **1a** was increased to 3 mmol (Scheme 4). The synthetic utility of the current method was demonstrated by applying it to the preparation of optically active phenyl-containing compounds (Scheme 4). The treatment of **2a** with methylmagnesium bromide gave methylated tertiary alcohol **4** in good yield, without a noticeable loss of ee. The effective reduction of **2a** by treatment with $NaBH_4$ gave secondary alcohol **5** in high yield with high diastereoselectivity.[18]

Conclusions

In summary, we have developed an asymmetric umpolung reaction of methyl ketones to prepare α-phenylated ketones with high enantioselectivities. This straightforward method provides rapid access to enantioenriched α-phenylated ketones *via* a simple operation. Further studies to improve the enantioselectivity and extend the catalytic protocol are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) P. J. Harrington and E. Lodewijk, *Org. Process Res. Dev.*, 1997, **1**, 72; (*b*) X. Chen, J. Z. M. Fong, J. Xu, C. Mou, Y. Lu, S. Yang, B.-A. Song and Y. R. Chi, *J. Am. Chem. Soc.*, 2016, **138**, 7212; (*c*) C. Chen, H. Wang, Z. Zhang, S. Jin, S. Wen, J. Ji, L. W. Chung, X.-Q. Dong and X. Zhang, *Chem. Sci.*, 2016, **7**, 6669.

2 (*a*) G. Castaldi, G. Barreca and A. Bologna, *WO* 03093276, Dinamite, Dipharma S.P.A., 2003; (*b*) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie and Q.-L. Zhou, *Nat. Chem.*, 2010, **2**, 546.

3 (*a*) R. Rometsch, *U.S. Patent*, 2838519, 1958; (*b*) M. Prashad, B. Hu, O. Repič, T. J. Blacklock and P. Giannousis, *Org. Process Res. Dev.*, 2000, **4**, 55.

4 (*a*) S. Lou and G. C. Fu, *J. Am. Chem. Soc.*, 2010, **132**, 1264; (*b*) P. M. Lundin, J. Esquivias and G. C. Fu, *Angew. Chem., Int. Ed.*, 2009, **48**, 154.

5 A. H. Cherney, N. T. Kadunce and S. E. Reisman, *J. Am. Chem. Soc.*, 2013, **135**, 7442.

6 (*a*) C. H. Cheon, O. Kanno and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 13248; (*b*) B. C. Kang, D. G. Nam, G.-S. Hwang and D. H. Ryu, *Org. Lett.*, 2015, **17**, 4810; (*c*) M. Brown, R. Kumar, J. Rehbein and T. Wirth, *Chem. – Eur. J.*, 2016, **22**, 4030; (*d*) R. Doran and P. J. Guiry, *J. Org. Chem.*, 2014, **79**, 9112.

7 For umpolung reactions at the α-carbon of carbonyl compounds, see: O. Miyata, T. Miyoshi and M. Ueda, *ARKIVOC*, 2013, 60.

8 For α-arylation of carbonyl compounds, see: (*a*) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234; (*b*) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676.

9 (*a*) T. Miyoshi, T. Miyakawa, M. Ueda and O. Miyata, *Angew. Chem., Int. Ed.*, 2011, **50**, 928; (*b*) T. Miyoshi, S. Sato, H. Tanaka, C. Hasegawa, M. Ueda and O. Miyata, *Tetrahedron Lett.*, 2012, **53**, 4188; (*c*) T. Miyoshi, N. Takeda, M. Fukami, S. Sato, M. Ueda and O. Miyata, *Chem. Pharm. Bull.*, 2014, **62**, 927; (*d*) R. K. Nandi, N. Takeda, M. Ueda and O. Miyata, *Tetrahedron Lett.*, 2016, **57**, 2269; (*e*) N. Takeda, E. Futaki, Y. Kobori, M. Ueda and O. Miyata, *Angew. Chem., Int. Ed.*, 2017, **56**, 16342.

10 For examples of asymmetric α-oxylation and α-amination of ketones and their equivalents see: (*a*) B. Basdevant and

C. Y. Legault, *Org. Lett.*, 2015, **17**, 4918; (*b*) P. Mizar and T. Wirth, *Angew. Chem., Int. Ed.*, 2014, **53**, 5993; (*c*) D. H. Miles, J. Guasch and F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 7632.

11 T. A. Targel, J. N. Kumar, O. S. Shneider, S. Bar, N. Fridman, S. Maximenko and A. M. Szpilman, *Org. Biomol. Chem.*, 2015, **13**, 2546.

12 (*a*) A. Abiko, O. Moriya, S. A. Filla and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 793; (*b*) H. Nemoto, R. Ma, T. Kawamura, M. Kamiya and M. Shibuya, *J. Org. Chem.*, 2006, **71**, 6038; (*c*) A. C. Evans, D. A. Longbottom, M. Matsuoka, J. E. Davis, R. Turner, V. Franckevičius and S. V. Ley, *Org. Biomol. Chem.*, 2009, **7**, 747; (*d*) A. C. Evans, D. A. Longbottom, M. Matsuoka and S. V. Ley, *Synlett*, 2005, 646; (*e*) A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1996, **37**, 1077.

13 (*a*) S.-M. Lu and C. Bolm, *Angew. Chem., Int. Ed.*, 2008, **47**, 8920; (*b*) T.-L. Liu, T. W. Ng and Y. Zhao, *J. Am. Chem. Soc.*, 2017, **139**, 3643.

14 The excess amount of Ph_3Al plays an important role in enamine formation because it can trap one equivalent of water which was *in situ* generated by the condensation reaction of **1a** and **3**.

15 Asymmetric α-phenylation of a diethylketone under the optimal reaction conditions gave an α-phenylated ketone in 74% yield with 45% ee, while α-phenylation of cyclohexanone gave the α-phenylated product in 64% yield with 34% ee. In addition, asymmetric α-phenylation of 2-hexanone afforded the corresponding α-phenylated product in 57% yield with 90% ee.

16 When **1a** was treated with tri(*p*-tolyl)aluminium in the presence of **3**, an α-(*p*-tolylated) ketone was obtained in 51% yield with 33% ee. An erosion of the enantioselectivity is probably caused by the effect of inorganic salt which was *in situ* generated during the preparation of tri(*p*-tolyl)aluminium ($3p$-tolylMgBr + $AlCl_3$ → p-tolyl$_3$Al + 3MgClBr).

17 The use of triethylaluminium for the asymmetric α-ethylation of **1a** gave a complex mixture. However, the reaction of **1a** with triisobutylaluminium in the presence of **3** gave 4-phenyl-2-butanol in 81% yield with 0% ee.

18 We have not yet been able to establish the relative stereochemistry of the major diastereomer.