Cooperative catalysis in highly enantioselective Mannich-type three-component reaction of a diazoacetophenone with an alcohol and an imine†

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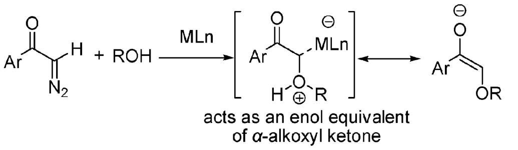
A highly enantioselective three-component reaction of a diazoacetophenone, an alcohol, and an imine catalyzed cooperatively by $Rh_2(OAc)_4$ and BINOL-derived chiral phosphoric acid has been developed for the synthesis of chiral β-amino-α-hydroxyl ketones in good yield with excellent diastereo and enantio selectivity.

The development of efficient methods for building polyfunctional chiral molecules from simple, readily available starting materials continues to be a challenge for organic chemists.[1] Enantioselective multicomponent reactions (MCRs) have received considerable attention because of the advantages of constructing chiral compounds from three or more precursors in one step in an efficient and atom-economic way, and much progress has been made in recent years.[2] Management of the reaction selectivity, especially the enantioselectivity, of MCRs is quite challenging because of the increased number of possible conformations in transition states that contain three or more precursors.[3]

Transition metal catalyzed diazo decomposition reactions *via* metal carbenoid intermediates have a broad range of uses in organic synthesis,[4] including their recent application to asymmetric MCRs.[5] Davies and Beckwith classified carbenoid intermediates into three major groups according to the carbenoid functionality.[6] It has been shown that donor/acceptor carbenoids offer many synthetic advantages over conventional carbenoids because of the balanced reactivity and selectivity of these carbenoids. Excellent enantioselective control has been achieved in a number of catalytic reactions using donor/acceptor carbenoids.[5a–c,7] However, because of the high reactivity of acceptor carbenoids such as those derived from diazoacetophenone, it has been extremely difficult to achieve high levels of enantioselective control in transition metal catalyzed asymmetric reactions.[8]



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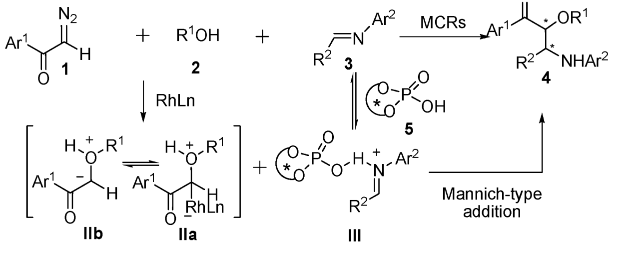
In this study, we report a highly enantioselective Mannich-type three-component reaction involving diazo decomposition of diazoacetophenones. A cooperative catalysis strategy[9] is applied to achieve high-level control of the reaction selectivity. A diazoacetophenone and an alcohol served as the enol equivalent of an α-alkoxyl aryl ketone[10] by forming an oxonium ylide in the presence of an $Rh_2(OAc)_4$ catalyst (eqn (1)), and a chiral Brønsted acid co-catalyst was introduced to control the reaction selectivity by activating an imine component. Because of the "buffered" reactivity of the acceptor carbenoid as a result of ylide formation, high enantioselectivity can be achieved in the subsequent imine addition. The advantage of the three-component reaction suggests that a considerable variety of optically active α-alkoxyl-β-amino ketones bearing two adjacent chiral centers can be assembled from three simple materials (Scheme 1).

At the outset, we were aware of some potential difficulties that we might encounter in using a Brønsted acid as the co-catalyst in this Mannich-type addition of oxonium ylides to imines. In addition to the O–H insertion side reaction, other two-component side reactions such as aziridination,[11] and Mannich-type addition of diazo compounds to imines[12] may compete with the desired three-component reaction. Despite these concerns, we carried out the three-component reaction in the presence of an $Rh_2(OAc)_4$ catalyst and a chiral Brønsted acid co-catalyst, in the hope that the co-catalytic system would help the intrinsic reaction kinetics, leading to the desired three-component pathway.

We first investigated a model reaction using a diazoacetophenone **1a**, 9-anthryl alcohol **2a**, and *N*-phenylbenzaldehyde imine **3a** at 0 °C with a variety of chiral phosphoric acids as co-catalyst. As shown in Table 1, the reaction gave a low yield of the desired coupling product with an excellent diastereomeric ratio (dr) and moderate enantiomeric excess (ee) (entries 1–10). No side products derived from two-component aziridination or Mannich reactions were observed. Instead, the major byproduct was derived from O–H insertion to give α-(9-anthracenylmethoxy)-acetophenone **(6)**.[13] By extensive



Scheme 1 Three-component reaction of a diazoacetophenone with an alcohol and an imine.

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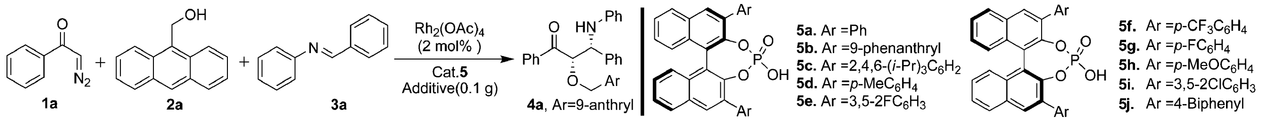
Table 1 Catalyst screening and reaction condition optimization for the three-component Mannich-type reaction[a]



Entry	Cat. **5** (mol%)	Additive	Solvent	T/°C	Yield[b] (%)	dr[c]	ee[d] (%)
1	**5a** (2)	4 Å MS	DCM	0	25	> 97 : 3	52
2	**5b** (2)	4 Å MS	DCM	0	30	> 97 : 3	70
3	**5c** (2)	4 Å MS	DCM	0	26	> 97 : 3	61
4	**5d** (2)	4 Å MS	DCM	0	15	> 97 : 3	57
5	**5e** (2)	4 Å MS	DCM	0	23	> 97 : 3	60
6	**5f** (2)	4 Å MS	DCM	0	47	> 97 : 3	82
7	**5g** (2)	4 Å MS	DCM	0	29	> 97 : 3	47
8	**5h** (2)	4 Å MS	DCM	0	38	> 97 : 3	41
9	**5i** (2)	4 Å MS	DCM	0	33	> 97 : 3	55
10	**5j** (2)	4 Å MS	DCM	0	27	> 97 : 3	61
11	**5f** (5)	5 Å MS	Toluene	25	85	> 97 : 3	90

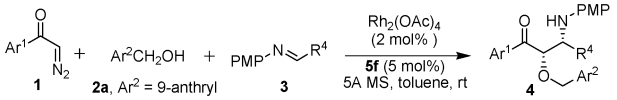
[a] Unless otherwise noted, the reaction was carried out on a 0.2 mmol scale and **1a** : **2a** : **3a** = 1.2 : 1.0 : 1.0. [b] Isolated yield of **4a**. [c] The dr ratio was determined by ^{1}H NMR spectroscopy from a crude reaction mixture. [d] The ee value was determined by chiral HPLC.

reaction condition optimization, we found that the best result was achieved under the following reaction conditions: 5 mol% of **5f** as the co-catalyst, 5 Å molecular sieve (MS) as an additive, toluene as the solvent, and a reaction temperature of 25 °C; these conditions gave the desired product **4a** in 85% yield with greater than 20 : 1 dr and 90% ee (entry 11).

Once we had obtained this preliminary result, the effect of *N*-substitution (*N*-Ar) of the imine **3** on the reaction was evaluated. There was no significant effect on the ee with electron-donating imines. Thus, the generality of the protocol was investigated in detail for various diazo compounds and imines derived from *p*-MeO-aniline (Table 2). With both electron-rich and electron-poor imines, the reactions generally proceeded smoothly, furnishing the corresponding *syn*-β-amino-α-hydroxyl ketones with excellent dr and ee (entries 1–6). The reaction is a little sensitive to the steric effects of the imine used. When imines derived from *ortho*-substituted aromatic aldehydes were used, the diastereoselectivity decreased significantly (entries 8 and 9). It is worth mentioning that the imine **3n** generated *in situ* from a cyclohexyl aldehyde was equally effective, providing the desired product *syn*-**4p** in 68% yield with 93% ee (entry 11); this demonstrates that the reaction scope can be extended to alkylimines. In the case of diazo compounds **1b**–**1d**, the reaction with imine **3h** proceeded smoothly, affording the corresponding product in good yield and with a high level of stereoselective control (entries 12–14).

A control experiment was carried out to exclude the possibility that the coupling products **4** were formed from the O–H insertion product **6** *via* a stepwise reaction pathway. The reaction of imine **3b** with **6** resulted no trace amount of the three-component coupling product **4b** under the same reaction conditions as that of the three-component reaction.[13] In the current three-component reaction, the desired products **4** can only be formed when the three precursors are concurrent, and in the presence of the two catalysts operated cooperatively.

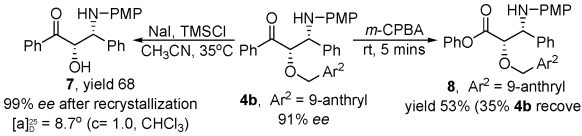
Table 2 Enantioselective three-component reaction of 9-anthryl alcohol (**2a**) with various diazo compounds **1** and imines **3**[a]



Entry	**1** (Ar^1)	**3** (R^4)	**4**	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a** (Ph)	**3b** (Ph)	**4b**	88	> 97 : 3	91
2	**1a** (Ph)	**3e** (p-MeC$_6$H$_4$)	**4c**	83	> 97 : 3	92
3	**1a** (Ph)	**3f** (p-FC$_6$H$_4$)	**4d**	78	> 97 : 3	92
4	**1a** (Ph)	**3g** (p-ClC$_6$H$_4$)	**4e**	73	> 97 : 3	98
5	**1a** (Ph)	**3h** (p-BrC$_6$H$_4$)	**4f**	70	> 97 : 3	93
6	**1a** (Ph)	**3i** (p-CF$_3$C$_6$H$_4$)	**4g**	75	> 97 : 3	90
7	**1a** (Ph)	**3j** (m-BrC$_6$H$_4$)	**4h**	76	> 97 : 3	92
8	**1a** (Ph)	**3k** (o-BrC$_6$H$_4$)	**4i**	82	80 : 20	90/63
9	**1a** (Ph)	**3l** (o-CF$_3$C$_6$H$_4$)	**4j**	73	83 : 17	80/75
10	**1a** (Ph)	**3m** (3,4-Cl$_2$C$_6$H$_3$)	**4k**	71	> 97 : 3	93
11[e]	**1a** (Ph)	**3n** (cyclohexyl)	**4l**	68	> 97 : 3	93
12	**1b** (p-ClC$_6$H$_4$)	**3h** (p-BrC$_6$H$_4$)	**4m**	67	> 97 : 3	94
13	**1c** (m-BrC$_6$H$_4$)	**3h** (p-BrC$_6$H$_4$)	**4n**	77	> 97 : 3	92
14	**1d** (o-BrC$_6$H$_4$)	**3h** (p-BrC$_6$H$_4$)	**4o**	74	> 97 : 3	87

[a] For conditions, see ESI.† [b] Isolated yield of **4**. [c] The dr ratio was determined by ^{1}H NMR spectroscopy from a crude reaction mixture. [d] The ee value was determined by chiral HPLC. [e] Imine **3n** was formed *in situ* from the corresponding amine and aldehyde.

Mannich-type adducts are valuable synthetic intermediates. Cleavage of the 9-anthryl auxiliary from the ketone product **4b** was accomplished using an optimized oxidation process with NaI/TMSCl, providing the free O–H compound **7** in 68% yield.[14] The relative and absolute stereochemistry of **7** was determined as (2*S*,3*R*) in agreement with data previously reported in the literature.[15] Oxidation with *m*-CPBA generated β-amino-α-hydroxyl ester **8** in 53% yield with 35% starting material **4b** recovered (eqn (2)).[13,16]



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In summary, we have developed a novel enantioselective three-component Mannich-type reaction of a diazoacetophenone, an alcohol, and an imine co-catalyzed by $Rh_2(OAc)_4$ and a chiral Brønsted acid. Optically active β-amino-α-hydroxyl ketones have been prepared with excellent diastereoselectivity and enantioselectivity from three simple starting materials in one reaction. Successful use of acceptor carbenoids derived from diazoacetophenones in the coupling reaction indicates that the cooperative catalysis strategy may be applicable to other acceptor diazo compounds to achieve a high level of control of the reaction selectivity. Research is currently underway to further expand the reaction scope, as well as to demonstrate the use of this methodology in the synthesis of biologically active compounds.

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Notes and references

1 For reviews: (*a*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*b*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*c*) B. A. Arndtsen, *Chem.–Eur. J.*, 2009, **15**, 302; (*d*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (*e*) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (*f*) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (*g*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (*h*) J. Zhu and H. Bienaymé, *Multicomponent reactions*, Wiley-VCH, Weinheim, 2005.

2 Selected examples of recent progress in AMCRs: (*a*) N. J. A. Martin and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13368; (*b*) H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.*, 2009, **131**, 4598; (*c*) S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen and K. A. Jøgensen, *Angew. Chem., Int. Ed.*, 2008, **47**, 121; (*d*) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84; (*e*) J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 2458; (*f*) M. Yamanaka, I. Junji, K. Fuchibe and T. Akiyama, *J. Am Chem. Soc.*, 2007, **129**, 6756.

3 (*a*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; (*b*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*c*) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*d*) A. Dondoni and A. Massi, *Acc. Chem. Res.*, 2006, **39**, 451.

4 For review: (*a*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*b*) A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341; (*c*) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; (*d*) M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley & Sons, New York, 1998; (*e*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704.

5 (*a*) X.-Y. Guan, L.-P. Yang and W.-H. Hu, *Angew. Chem., Int. Ed.*, 2010, **49**, 2190; (*b*) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782; (*c*) X. Zhang, H.-X. Huang, X. Guo, X.-Y. Guan, L.-P. Yang and W.-H. Hu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6647; (*d*) S. Torssell, M. Kienle and P. Somfai, *Angew. Chem., Int. Ed.*, 2005, **44**, 3096.

6 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861.

7 Highly enantioselective reactions with donor/acceptor carbenoids: 3 + 2 annulation: (*a*) Y.-J. Lian and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 440; Cyclopropanation: (*b*) J. L. Thompson and H. M. L. Davies, *J. Am. Chem. Soc.*, 2007, **129**, 6090; (*c*) Y. Chen, J. V. Ruppel and X. P. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 12074; (*d*) J. R. Denton and H. M. L. Davies, *Org. Lett.*, 2009, **11**, 787; XH-insertion: (*e*) S.-F. Zhu, C. Chen, Y. Cai and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2008, **47**, 932; (*f*) E. C. Lee and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 12066; (*g*) Z.-J. Li and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 396; (*h*) H. M. L. Davies, C. Venkataramani, T. Hansen and D. W. Hopper, *J. Am. Chem. Soc.*, 2003, **125**, 6462.

8 Selected enantioselective reactions from diazoacetophenone: (*a*) M. Barberis, J. Prieto, S. Stiriba and P. Lahuerta, *Org. Lett.*, 2001, **3**, 3317; (*b*) I. Nicolas, T. Roisnel, P. L. Maux and G. Simonneaux, *Tetrahedron Lett.*, 2009, **50**, 5149; (*c*) D. J. Wardrop and R. E. Forslund, *Tetrahedron Lett.*, 2002, **43**, 737; (*d*) J. R. Denton and H. M. L. Davies, *Org. Lett.*, 2009, **11**, 787; (*e*) P. Müller and P. Polleux, *Helv. Chim. Acta*, 1994, **77**, 645; (*f*) M. P. Doyle, M. Y. Eismont and Q.-L. Zhou, *Russ. Chem. Bull.*, 1997, **46**, 955; (*g*) P. Müller and E. Maitrejean, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1807.

9 For cooperative catalysis to enhance reaction selectivity, see reviews: (*a*) H. Yamamoto and K. Futatsugi, *Angew. Chem., Int. Ed.*, 2005, **44**, 1924; (*b*) J. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*c*) Y. J. Park, J. Park and C. Jun, *Acc. Chem. Res.*, 2008, **41**, 222; (*d*) Z.-H. Shao and H.-B. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745; (*e*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422; selected examples: (*f*) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (*g*) T. Yang, A. Ferrali, L. Campbell and D. J. Dixon, *Chem. Commun.*, 2008, 2923; (*h*) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182; (*i*) B. M. Trost, E. J. McEachern and F. D. Toste, *J. Am. Chem. Soc.*, 1998, **120**, 12702; (*j*) M. Terada and Y. Toda, *J. Am. Chem. Soc.*, 2009, **131**, 6354.

10 Selected examples of recent progress using α-alkoxyl arylketone as Mannich donor: (*a*) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 3470; (*b*) D. Enders, C. Grondal, M. Vrettou and G. Raabe, *Angew. Chem., Int. Ed.*, 2005, **44**, 4079; (*c*) S. S. V. Ramasastry, H.-L. Zhang, F. Tanaka and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2007, **129**, 288; (*d*) L.-L. Cheng, X. Han, H.-M. Huang, M. W. Wonga and Y.-X. Lu, *Chem. Commun.*, 2007, 4143.

11 (*a*) T. Hashimoto, N. Uchiyama and K. Maruoka, *J. Am. Chem. Soc.*, 2008, **130**, 14380; (*b*) Z.-J. Lu, Y. Zhang and W. D. Wulff, *J. Am. Chem. Soc.*, 2007, **129**, 7185; (*c*) T. Hashimoto, N. Uchiyama and K. Maruoka, *J. Am. Chem. Soc.*, 2008, **130**, 14380; (*d*) M. P. Doyle, W.-H. Hu and D. J. Timmons, *Org. Lett.*, 2001, **3**, 933.

12 (*a*) T. Hashimoto and K. Maruoka, *Synthesis*, 2008, 3703; (*b*) T. Hashimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2007, **129**, 10054.

13 See ESI†.

14 (*a*) A. O. George, C. N. Subhash, G. B. G. Balaram and M. Ripudaman, *J. Org. Chem.*, 1979, **44**, 1247; (*b*) E. J. Michael and A. L. Mark, *J. Org. Chem.*, 1977, **42**, 3761.

15 Lit. $[\alpha]_D^{25} = -9.58°$ (c = 0.748, CHCl$_3$, 99% ee), see: B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338.

16 (*a*) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 8777; (*b*) M. B. Andrus, E. J. Hicken, J. C. Stephens and D. K. Bedke, *J. Org. Chem.*, 2005, **70**, 9470.