

Selectivity control in enantioselective four-component reactions of aryl diazoacetates with alcohols, aldehydes and amines: an efficient approach to synthesizing chiral β -amino- α -hydroxyesters†

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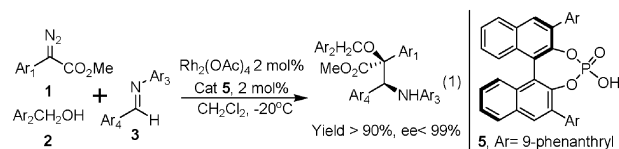
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Enantioselective four-component reactions of aryl diazoacetates with alcohols, aldehydes and amines catalyzed cooperatively by a rhodium complex and a chiral Brønsted acid produce β -amino- α -hydroxy acid derivatives in a single step with excellent control of chemo-, diastereo- and enantioselectivity.

β -Amino- α -hydroxy acids are very useful building blocks and important pharmacophores in numerous bioactive natural products that display antitumor, antibiotic, or antifungal properties.¹ In addition, compounds of this family are incorporated into many biologically active peptides, such as amastatin, bestatin, BACE1 amyloid, and aminopeptidases.² Particularly, the presence of a quaternary stereocenter in a highly substituted β -amino acid unit, which is characterized by a conformational constraint, will interact with certain proteases and resist proteolytic degradation.³

In recent years, much attention has been devoted to the synthesis of chiral β -amino- α -hydroxy acid core structures.⁴ However, most of the synthetic approaches are multi-step reactions. Recently, our group reported an enantioselective three-component single step reaction in which an *in situ* generated oxonium ylide is trapped by an imine to give the β -amino- α -hydroxy acid derivatives bearing a quaternary stereogenic carbon center (Scheme 1).⁵ Since the imine could be generated *in situ* from corresponding aldehyde and amine, we envisioned that by optimizing reaction conditions, it should be possible to conduct a four-component reaction of a diazoacetate and an alcohol with the aldehyde and the amine. Advantages of such an approach include: (1) reducing by one step the imine preparation; (2) facilitating the preparation of imines that are otherwise difficult to synthesize in a pure form due to the reversibility of their formation; and (3) increasing the flexibility of manipulation for rapid building of a large library of compounds. These advantages have been widely demonstrated in the literature.⁶

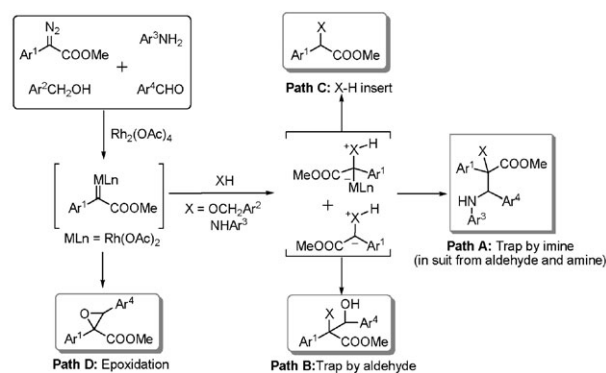
The multicomponent reactions (MCRs) offer substantial advantages over the traditional approach because they often use smaller quantities of reagents and reduce the time and effort required.⁷ The modular character of MCRs is also suitable for drug discovery, and it is therefore widely used for the fast generation of bioactive compounds.⁸ However, one of the most challenging issues associated with multi-component reactions is chemoselectivity control. This is particularly difficult in the



Scheme 1

current four-component ylide trapping process because there are several ylide intermediates that can irreversibly lead to undesired side products in the reaction. Since imine formation is a reversible process, the presence of unreacted amine and corresponding aldehyde increases the complexity of the reaction (Scheme 2). In addition to our desired reaction pathway of trapping the protonated oxonium ylide with the *in situ* generated imine (path A), possible side reaction pathways include: (1) trapping of onium ylides with the aldehyde (path B);⁹ (2) O–H insertion and N–H insertion (path C);¹⁰ and (3) epoxidation of the aldehyde (path D).¹¹

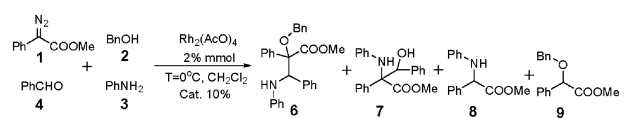
We envisioned that a Brønsted acid would play a dual role in the current reaction. First, it would accelerate the imine formation, and second, it would activate the imine by iminium formation to be a more reactive electrophile to trap the oxonium ylide. Both effects of the acid additive would favor the reaction kinetics of the desired reaction pathway A. To validate this hypothesis, we screened a number of acid additives in the four-component reaction of methyl phenyldiazoacetate, benzyl alcohol, benzaldehyde and aniline. The results of this reaction are summarized in Table 1. A control reaction in the absence of an acid additive was conducted. Inherent reaction kinetics led to a mixture of four compounds **6–9**, from which the desired four-component product **6** was isolated with a less than 10% yield (entry 1). As anticipated, acid additives



Scheme 2 Possible pathways of the four-component reaction.

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Table 1 Optimization of chemoselective four-component reactions^a

Entry	Cat.	Yield (%) ^b	6 : 7 : 8 : 9	Dr (6) ^c
1	—	< 10	22 : 7 : 54 : 17	78 : 22
2	PhCOOH	< 10	10 : 0 : 36 : 54	—
3	AcOH	21	25 : 0 : 21 : 54	70 : 30
4	TFA	33	75 : 0 : 10 : 15	83 : 17
5	TMSOTf	32	49 : 0 : 33 : 18	62 : 38
6	TsOH	57	78 : 0 : 5 : 17	81 : 19
7 ^d	TsOH	56	76 : 0 : 6 : 18	82 : 18

^a Unless otherwise noted, the reaction was carried out on a 0.25 mmol scale and **4** (0.30 mmol) and **1** (0.275 mmol) were added to the mixture in 1 h. ^b Isolated yield of **6**. ^c Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^d 1.5 eq. of **4** was added.

increased the chemoselectivity (entries 2–6). TsOH was identified as the best acid catalyst among those screened, as the desired product **6** was isolated with a 57% yield with 81 : 19 diastereoselectivity favoring the *syn*-isomer (entry 6). The concept of combining a metal and an organic catalyst to broaden reaction scope has been previously demonstrated in the literature.¹²

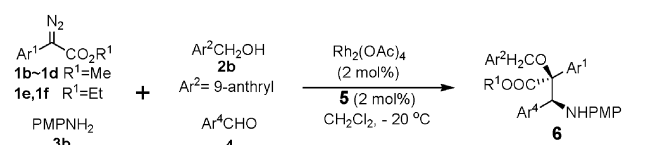
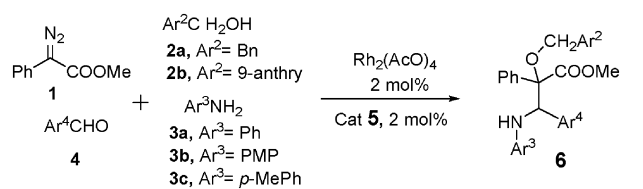
Our next effort was to incorporate a chiral Brønsted acid to achieve the enantioselective four-component reaction, taking advantage of our previous study of the enantioselective three-component reaction. Chiral phosphoric acid **5** was employed as the chiral catalyst of choice. The four-component reaction was promoted by the chiral phosphoric acid (Table 2, entry 1), and the bulky alcohol **2b** significantly increased the dr value to 99 : 1 and the ee value to greater than 81% (entry 2). The ee value increased to 91% at a lower reaction temperature (entry 3). *p*-Anisidine **3b** was superior to aniline and 4-toluidine in

terms of giving higher ee (entries 3 vs. 4 and 7 vs. 8). The reaction appears less sensitive to the electronic effect of the aldehyde (entries 4–7).

Using the above optimized reaction conditions, the reaction scope was extended to additional substrates, with the results summarized in Table 3. In most cases, only *syn*-products were obtained with an ee greater than 90% and moderate to good yields. Aldehydes with *o*-, *m*-, or *p*-substituted, electron-poor or electron-rich (entries 1–7), and even bulky aldehydes (entries 8 and 9) are all tolerated. *p*-Substituted aryldiazo compounds were superior to *o*- and *m*-substituted substrates (entries 10–12). In addition, ethyl aryldiazo compounds (entries 13 and 14) and ethyl *trans*-styryldiazoacetate (entry 15) gave the desired product with an excellent ee. When cyclohexyl formaldehyde was employed, the ee dropped to 49%, with a lower yield under the current reaction conditions (entry 16).

For insight into the role of phosphoric acid in promoting the imine formation, we conducted a control reaction in a NMR tube. While 95% conversion of the imine from benzaldehyde and aniline was achieved within 5 min in the presence of 2 mol% **5**, the same conversion was achieved only after more than 24 hours in the absence of the acid catalyst (see ESI†).

The proposed reaction mechanism is shown in Scheme 3. The reaction proceeds through oxonium ylide intermediates **IIa** or **IIb**, which are generated *in situ* from carbenoid **I** and **2**. The intermediates **IIa/IIb** are trapped by electrophilic imines generated *in situ* from aldehydes and amines, leading to the optically active product **6**.

Table 3 Enantioselective four-component reactions of alcohol **2b** with various diazo compounds **1**, amines **3** and aldehydes **4**^a**Table 2** The enantioselectivity of the four-component reactions^{a,b}

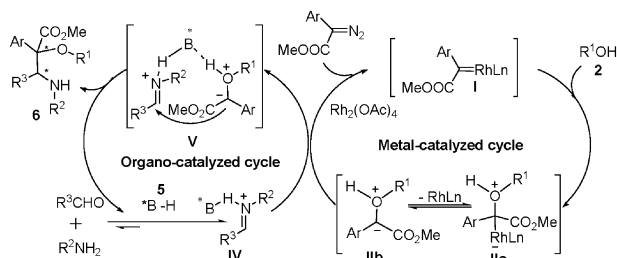
Entry	2/3	4 (Ar ⁴)	T (°C)	6	Yield (%) ^c	Dr ^d	Ee (%) ^e
1	2a/3a	Ph	0	6a	58	81 : 19	48
2	2b/3a	Ph	0	6b	72	> 99 : 1	81
3	2b/3a	Ph	–20	6b	82	> 99 : 1	91
4	2b/3b	Ph	–20	6c	83	> 99 : 1	94
5	2b/3b	<i>o</i> -NO ₂ C ₆ H ₄	–20	6d	81	82 : 18	92
6	2b/3b	<i>p</i> -ClC ₆ H ₄	–20	6e	92	> 99 : 1	94
7	2b/3b	<i>o</i> -BrC ₆ H ₄	–20	6f	96	> 99 : 1	97
8	2b/3c	<i>p</i> -BrC ₆ H ₄	–20	6g	85	95 : 5	93

^a Unless otherwise noted, the reaction was carried out in 0.25 mmol scale with **1/2/3/4** = 1.1/1/1/1.2, and **4** Å MS (0.1 g) was added.

^b PMP = *p*-methoxyphenyl. ^c Isolated yield. ^d Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^e Determined by chiral HPLC.

Entry	Ar ¹ (1)	Ar ⁴ (4)	6	Yield (%) ^b	Dr ^c	Ee (%) ^d
1	PMP (1a)	<i>p</i> -ClC ₆ H ₄	6h	72	> 99 : 1	95
2	PMP (1a)	Ph	6i	79	> 99 : 1	97
3	PMP (1a)	<i>m</i> -MeC ₆ H ₄	6j	62	> 99 : 1	92
4	PMP (1a)	<i>p</i> -MeC ₆ H ₄	6k	54	> 99 : 1	91
5	PMP (1a)	<i>o</i> -BrC ₆ H ₄	6l	79	> 99 : 1	95
6	PMP (1a)	<i>m</i> -BrC ₆ H ₄	6m	61	> 99 : 1	97
7	PMP (1a)	<i>p</i> -BrC ₆ H ₄	6n	90	> 99 : 1	95
8	PMP (1a)		6o	42	> 99 : 1	96
9	PMP (1a)		6p	68	> 99 : 1	92
10	<i>p</i> -BrC ₆ H ₄ (1b)	Ph	6q	78	> 99 : 1	93
11	<i>m</i> -ClC ₆ H ₄ (1c)	<i>p</i> -BrC ₆ H ₄	6r	75	> 99 : 1	87
12	<i>o</i> -BrC ₆ H ₄ (1d)	<i>p</i> -BrC ₆ H ₄	6s	58	> 99 : 1	81
13	PMP (1e)	<i>p</i> -BrC ₆ H ₄	6t	87	> 99 : 1	91
14	PMP (1e)	<i>o</i> -BrC ₆ H ₄	6u	90	> 99 : 1	97
15	<i>trans</i> -styryl (1f)	<i>p</i> -BrC ₆ H ₄	6v	28	> 99 : 1	95
16	PMP (1a)	Cyclohexyl	6w	34	95 : 5	49

^a For conditions, see ESI†. ^b Isolated yield. ^c Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^d Determined by chiral HPLC.



Scheme 3 Proposed mechanism of metal-organocatalytic cooperative catalysis.

In summary, we report an enantioselective four-component reaction of diazo compounds, alcohols, aldehydes, and amines in the presence of $\text{Rh}_2(\text{OAc})_4$ and co-catalyzed by a chiral Brønsted acid. The nature of the current four-component reaction is irreversible trapping of one intermediate (reversibly formed from two components) by another intermediate (reversibly formed from two additional components). The chiral acid catalyst plays multiple roles to drive the reaction kinetics to the desired product, a *syn* β -amino- α -hydroxyl acid derivative bearing a quaternary carbon stereogenic center, with high chemoselectivity and excellent diastereo- and enantioselectivity.

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Notes and references

- (a) A. Stöckel-Maschek, B. Stiebitz, R. Koelsch and K. Neuberta, *Bioorg. Med. Chem.*, 2005, **13**, 4806; (b) S. Sato, M. Tetsuhashi, K. Sekine, H. Miyachi, M. Naito, Y. Hashimoto and H. Aoyama, *Bioorg. Med. Chem.*, 2008, **16**, 4685; (c) D. L. Vaux and A. Strasser, *Proc. Natl. Acad. Sci. U. S. A.*, 1996, **93**, 2239; (d) C. L. Senese and A. J. Hopfinger, *J. Chem. Inf. Comput. Sci.*, 2003, **43**, 1297.
- (a) J. K. Ekegren, T. Unge, M. Z. Safa, H. Wallberg, B. Samuelsson and A. Hallberg, *J. Med. Chem.*, 2005, **48**, 8098; (b) C. Debouck and B. W. Metcalf, *Drug Dev. Res.*, 1990, **21**, 1.
- (a) J. K. Ekegren, T. Unge, M. Z. Safa, H. Wallberg, B. Samuelsson and A. Hallberg, *J. Med. Chem.*, 2005, **48**, 8098; (b) A. Guerrini, G. Varchi, C. Samor, R. Daniele and B. Arturo, *Tetrahedron Lett.*, 2007, **48**, 5081.
- (a) S. Abele and D. Seebach, *Eur. J. Org. Chem.*, 2000, **1**; (b) H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8180; (c) T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 2002, **67**, 7819; (d) A. A. Fuller, B. Chen, A. R. Minter and A. K. Mapp, *J. Am. Chem. Soc.*, 2005, **127**, 5376; (e) Y. Suto, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 500; (f) R. R. Müller, H. H. Goesmann and H. Waldmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 184; (g) B. D. Feske, *Curr. Org. Chem.*, 2007, **11**, 483; (h) L. Deng and E. N. Jacobsen, *J. Org. Chem.*, 1992, **57**, 4320; (i) L. Deng, E. N. Jacobsen, Y. Furukawa and L. E. Martinez, *Tetrahedron*, 1994, **50**, 4323.
- 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.
- (a) G. F. Ross, E. Herdtweck and I. Ugi, *Tetrahedron*, 2002, **58**, 6127; (b) S. Gedej, J. V. der Eycken and F. Fülöp, *Org. Lett.*, 2002, **4**, 1967; (c) A. Demharter, W. Horl, E. Herdtweck and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 173; (d) J. M. McFarland, N. S. Joshi and M. B. Francis, *J. Am. Chem. Soc.*, 2008, **130**, 7639; (e) Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu and L.-Z. Gong, *J. Am. Chem. Soc.*, 2007, **129**, 3790; (f) J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498; (g) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2006, **128**, 14802; (h) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84.
- (a) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 563; (b) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (c) *Multicomponent reactions*, ed. J.-P. Zhu and H. Bienaymé, Wiley, Weinheim, 2005; (d) P. Wipf, C. R. J. Stephenson and K. Okumura, *J. Am. Chem. Soc.*, 2003, **125**, 14694; (e) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Reekent and L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899; (f) J.-P. Zhu, *Eur. J. Org. Chem.*, 2003, **7**, 1133; (g) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (h) A. Shaabani, E. Soleimani, A. H. Rezayan, A. Sarvary and H. R. Khavasi, *Org. Lett.*, 2008, **10**, 2581; (i) Y. Mii, J. V. Schreiber and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 11290.
- (a) A. Dondoni and A. Massi, *Acc. Chem. Res.*, 2006, **39**, 451; (b) G. Guillena, D. J. Ramon and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693; (c) A. Alizadeh and N. Zohreh, *Helv. Chim. Acta*, 2008, **91**, 844; (d) S. D. Sharma, P. Hazarika and D. Konwar, *Tetrahedron Lett.*, 2008, **49**, 2216; (e) J.-Q. Wei and J. T. Shaw, *Org. Lett.*, 2007, **9**, 4077; (f) L.-J. Fan, E. Lobkovsky and B. Ganem, *Org. Lett.*, 2007, **9**, 2015; (g) A. S. Karpov, E. Merkul, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 6951; (h) O. Jiménez, G. de la Rosa and R. Lavilla, *Angew. Chem., Int. Ed.*, 2005, **44**, 6521; (i) P. Cristau, J.-P. Vors and J.-P. Zhu, *Org. Lett.*, 2001, **3**, 4079.
- (a) C.-D. Lu, Z.-Y. Chen, H. Liu, W.-H. Hu and A.-Q. Mi, *Org. Lett.*, 2004, **6**, 3071; (b) X. Zhang, H.-X. Huang, X. Guo, X.-Y. Guan, L.-P. Yang and W.-H. Hu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6647; (c) X. Guo, H.-X. Huang, L.-P. Yang and W.-H. Hu, *Org. Lett.*, 2007, **9**, 4721; (d) Y.-H. Wang, Z.-Y. Chen, A.-Q. Mi and W.-H. Hu, *Chem. Commun.*, 2004, 2486; (e) C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu and A.-Q. Mi, *Chem. Commun.*, 2005, 2624.
- (a) T. C. Maier and G. C. Fu, *J. Am. Chem. Soc.*, 2006, **128**, 4594; (b) E. C. Lee and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 12066; (c) B. Liu, S.-F. Zhu, W. Zhang, C. Chen and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 5834; (d) C. Chen, S.-F. Zhu, B. Liu, L.-X. Wang and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 12616.
- (a) S. Son and G. C. Fu, *J. Am. Chem. Soc.*, 2007, **129**, 1046; (b) S. J. Hedley, D. L. Ventura, P. M. Dominiak, C. L. Nygren and H. M. L. Davies, *J. Org. Chem.*, 2006, **71**, 5349; (c) Q.-G. Wang, X.-M. Deng, B.-H. Zhu, L.-W. Ye, X.-L. Sun, C.-Y. Li, C.-Y. Zhu, Q. Shen and Y. Tang, *J. Am. Chem. Soc.*, 2008, **130**, 5408.
- (a) B. G. Jellerichs, J.-R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 7758; (b) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (c) I. Ibrahim and A. Cordova, *Angew. Chem., Int. Ed.*, 2006, **45**, 1952; (d) V. Komanduri and M. J. Krische, *J. Am. Chem. Soc.*, 2006, **128**, 16448; (e) S. Chercheja and P. Eilbracht, *Adv. Synth. Catal.*, 2007, **349**, 1897; (f) G. Chen, Y. Deng, L. Gong, A. Mi, X. Cui, Y. Jiang, M. C. K. Choi and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2001, **12**, 1567; (g) M. Nakoji, T. Kanayama, T. Okino and Y. Takemoto, *Org. Lett.*, 2001, **3**, 3329; (h) M. Nakoji, T. Kanayama, T. Okino and Y. Takemoto, *J. Org. Chem.*, 2002, **67**, 7418; (i) T. Kanayama, K. Yoshida, H. Miyabe and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2003, **42**, 2054; (j) For reviews: Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222; (k) T. Andrea and M. S. Eisen, *Chem. Soc. Rev.*, 2008, **37**, 550; (l) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science*, 2007, **317**, 496.