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# Diastereoselectively Switchable Enantioselective Trapping of Carbamate Ammonium Ylides with Imines

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Supporting Information

**ABSTRACT:** The diastereoselectively switchable enantioselective trapping of protic carbamate ammonium ylides with imines is reported. The intriguing $Rh_2(OAc)_4$ and chiral Brønsted acid cocatalyzed three-component Mannich-type reaction of a diazo compound, a carbamate, and an imine provides rapid and efficient access to both *syn*- and *anti*-α-substituted α,β-diamino acid derivatives with a high level control of chemo-, diastereo-, and enantioselectivity.

Secondary protic ammonium ylides[1] accommodating both acidic ammonium ion and basic carbon centers in close proximity are highly unstable and reactive intermediates, and have been proposed as the intermediates in N−H insertion reactions of amines with carbenes/carbenoids.[2] Surprisingly, recent studies in our laboratory showed that interception of the in situ generated protic ammonium ylides with appropriate carbon electrophiles before the 1,2-proton shift are viable.[3] These intriguing findings have challenged and changed the traditional perception of protic ammonium ylides, thus openning up new research directions. Trapping the protic ammonium ylides with appropriate electrophiles could provide quick accesses to a variety of structures.[3] However, these reactions have encountered several major restrictions: (1) only arylamines were effective in forming the active ylides for electrophilic trapping in catalytic settings, thus limiting their synthetic value; (2) poor chemo- and/or diastereoselectivity were observed; (3) no asymmetric version has been achieved. We now present our attempts to resolve these issues via a dual/cooperative catalysis strategy.[4]

The methyl phenyldiazoacetate (**1a**)/benzyl carbamate (**2a**)/phenylbenzylimine (**3a**) combination was chosen as the starting point for the three-component reaction (Figure 1). The carbamate **2a** was chosen instead of an arylamine as a component for the following reasons: (1) easy deprotection to form free amino compounds, and increased potential synthetic value; (2) the less-coordinating carbamate should not poison the transition-metal catalyst and should also be more compatible with other electrophiles such as aldehydes. However, there is a significant risk in using **2a** in the desired three-component reaction due to the decreased electron density of the nitrogen atom of **2a**. A concerted or near-concerted reaction pathway has been proposed in the intramolecular N−H insertion of carbamate BocNHR.[5] If this concerted N−H insertion occurred with **2a** in the current reaction, no ylide trapping product would be obtained.

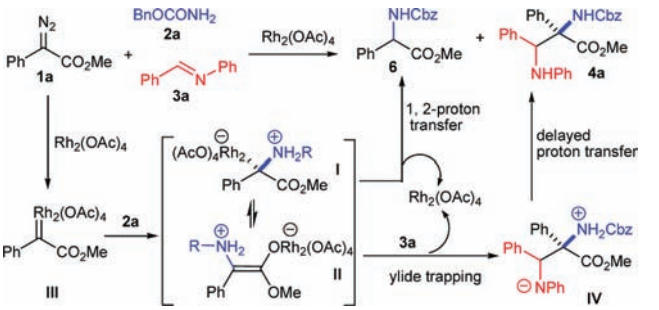


**Figure 1.** Proposed mechanism for the three component reaction of **1a**, **2a**, and **3a** catalyzed by $Rh_2(OAc)_4$.

Aware of the potential risks, we conducted the intermolecular ylide trapping reaction. A solution of diazo compound **1a** in 1, 2-dichloroethane (DCE) was slowly introduced into a mixture of **2a**, **3a**, and a catalytic amount of $Rh_2(OAc)_4$ in DCE over 1 h at 0 °C. We were gratified to find that the reaction gave **4a** in 30% yield with high diastereoselectivity (dr = 95:5), favoring the *anti* isomer. A significant amount of N−H insertion product **6** was isolated as a major side product. A control reaction indicated that **4a** was not derived from the N−H insertion side product **6**, since under identical reaction conditions, except that **3a** was added to the reaction mixture 1 h later, after complete decomposition of **1a**, only the N−H insertion product was obtained and no **4a** was detected.

The mechanism of rhodium carbenoid insertion into the carbamate N−H bond remains a controversial subject, and both concerted and stepwise (via metal-free or -associated ylide intermediates) processes are possibilities.[5] Our results strongly suggest a stepwise ylide trapping mechanism for the formation of **4a** and **6** (Figure 1). The protic carbamate ammonium ylides **I**/**II** underwent either 1,2-proton transfer to form N−H bond insertion product **6** or interception by an appropriate electrophile, such as imine **3a** in the current case, giving the first protic carbamate ammonium ylide trapping product **4a** via zwitterion **IV**, a process of "delayed proton transfer".

Pioneering work reported independently by the groups of Terada[6] and Akiyama[7] indicated that bifunctional chiral phosphoric acids (PPAs) are excellent Brønsted acid catalysts to activate imine substrates.[8] Recent advances in Brønsted acid activated electrophiles for carbon−carbon bond formation with

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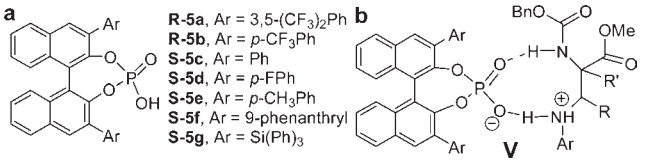


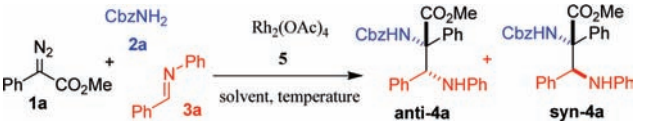

**Figure 2.** (a) Phosphoric acids. (b) Possible complex of phosphoric acid with the diamine product.

diazoalkanes have highlighted the compatibility of diazo compounds with Brønsted acid catalysis in organic reactions.[9] We envisioned that PPAs **5** (Figure 2a) would activate **3a** to be a more reactive electrophile toward carbamate ammonium ylides, while minimizing the 1,2-proton shift side product. This proved to be the case (Table 1); in the presence of 10 mol % **5** the yields increased dramatically up to 86% with a broad spectrum of reduced diastereoselectivities (83/17−15/85) (Table 1, entries 1−7).

The PPAs with electron-deficient 2,2′-aryl groups (**5a**, Ar = 3, 5-$(CF_3)_2$Ph; **5b**, Ar = *p*-$CF_3$Ph) afforded product mixtures with *anti*-**4a**/*syn*-**4a** ratios of 15/85 and 17/83, respectively, favoring the *syn* isomer. This is interesting in contrast with the *anti* selectivity in the reaction without PPA cocatalysts. The diastereoselectivity decreased slightly to 23/77 when a PPA with an electron-donating 2,2′-aryl group (**5e**, Ar = *p*-MePh) was used. Compared with the moderate electronic effects of a 2, 2′-aryl group in the PPA on the diastereoselectivities, the steric effect was more pronounced when **5f** (Ar = 9-phenanthryl) catalyzed the reaction, furnishing diamine **4a** with 38/62 dr, with increased *anti* selectivity. This trend is amazing, as the extremely bulky PPA **5g** (Ar = triphenylsilyl) resulted in a reversal of the dr to 83/17, favoring the *anti* diastereomer (Table 1, entry 7). The enantioselectivities of all the PPA-promoted reactions for the major isomer were quite high (68−94% ee).

To improve the performance of these dual catalysts that cooperatively catalyze multicomponent reactions, further optimization of the conditions was carried out. Toluene was very quickly identified as a better solvent than halogenated solvents (Table 1, entry 8: 87% yield, 95:5 dr, 92% ee). When we tried to decrease the catalyst loading of *S*-**5g** from 10 to 2 mol %, it was surprising to find that the ee for the major isomer *anti*-**4g** dropped significantly from 92% to 11% (Table 1, entry 9 vs 8). Since more basic diamine products may play a negative role in the reaction by sequestering the phosphoric acid via bidentate coordination (Figure 2b),[10] acidic additives should alleviate this effect by regenerating the acid catalyst.[11] L-Tartaric acid (20 mol %) was identified to be the most effective additive to this end when used along with **5g** (2 mol %), evidenced by enhanced yield and enantioselectivity (Table 1, entry 10 vs 9). Low temperatures were better, especially for the ee values manifested by the enantioselective outcomes of the reaction at 25 °C (77% ee) and −20 °C (93% ee) (Table 1, entry 13 vs 12). Thus the optimal conditions were established as 2 mol % $Rh_2(OAc)_4$, 5 mol % phosphoric acid **5g**, and 20 mol % tartaric acid in toluene at −20 °C (entry 13). Under these conditions, the protic ylide trapping reaction catalyzed by the less sterically hindered phosphoric acid **5a** also gave diamine **4a** in high yield and with excellent ee, but with the diastereoselective control switched in favor of the *syn* diastereomer (Table 1, entry 14). PPA only, tartaric acid only, and the PPA/tartaric acid combination all failed to promote this three-component reaction in the absence of the

**Table 1. Evaluation of Catalysts and Reaction Conditions**[a]




| entry | **5** (mol %) | solvent | *T* (°C) | yield (%)[b] | dr[c] *anti*/*syn* | Ee of *anti* (*syn*) (%)[c] |
|---|---|---|---|---|---|---|
| 1 | *R*-**5a** (10) | DCE | 0 | 78 | 15:85 | −9 (−94) |
| 2 | *R*-**5b** (10) | DCE | 0 | 76 | 17:83 | −4 (−78) |
| 3 | *S*-**5c**(10) | DCE | 0 | 76 | 22:78 | 24 (79) |
| 4 | *S*-**5d** (10) | DCE | 0 | 86 | 27:73 | 7 (77) |
| 5 | *S*-**5e** (10) | DCE | 0 | 81 | 23:77 | 16 (79) |
| 6 | *S*-**5f** (10) | DCE | 0 | 81 | 38:62 | 37 (89) |
| 7 | *S*-**5g** (10) | DCE | 0 | 78 | 83:17 | 68 (79) |
| 8 | *S*-**5g** (10) | PhMe | 0 | 87 | 95:5 | 92 |
| 9 | *S*-**5g** (2) | PhMe | 0 | 64 | 98:2 | 11 |
| 10[d] | *S*-**5g** (2) | PhMe | 0 | 80 | 96:4 | 81 |
| 11[d] | *S*-**5g** (5) | PhMe | 0 | 88 | 95:5 | 88 |
| 12[d] | *S*-**5g** (5) | PhMe | 25 | 92 | 82:8 | 77 |
| **13**[d] | *S*-**5g** (5) | **PhMe** | **−20** | **93** | **97:3** | **93** |
| **14**[d] | *R*-**5a** (5) | **PhMe** | **−20** | **90** | **10:90** | **(−96)** |
| 15[e] | *S*-**5g** (5) | PhMe | 0 | 85 | 93:7 | 90 |
| 16[d] | – | PhMe | 0 | 71 | 89:11 | 0.7 |

[a] Standard conditions: $Rh_2(OAc)_4$/**5**/**3a**/**2a** = 0.004/0.01/0.2/0.26 mmol, 4 Å molecular sieve (MS) (0.1 g); **1a** in 2.8 mL solvent was added under an argon atmosphere at 0 °C for 1 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] L-tartaric acid (20 mol %) was used. [e] DL-tartaric acid (20 mol %) was used.

Rh catalyst, indicating the critical role of the Rh catalyst in generating the metal carbenoid intermediate. Although chiral Brønsted acids have been shown to be effective in a number of asymmetric Mannich reactions, there has been no paper describing this exceptional inversion of diastereoselectivity simply by changing the steric nature of the 3,3′-BINOL substituents.[12]

The role of tartaric acid as an additive which could promote the turnover in the current reaction was further investigated. A control reaction in which L-tartaric acid was replaced by *rac*-tartaric acid delivered the same level of yield, dr, and ee (Table 1, entry 15). In addition, in the absence of a phosphoric acid, the reaction gave rise to negligible enantioselectivity and a decreased yield (Table 1, entry 16), suggesting a unique function of the phosphoric acids. In the absence of the acid additive, the reaction catalyzed by 2% **5g** gave only 11% ee; whereas, in the presence of 50% tartaric acid, the corresponding reaction delivered 81% ee. This huge 70% ee divergence diminished quickly on increasing the amount of **5g** alone to 10 mol % and disappeared completely when 20 mol % **5g** was used (see Supporting Information (SI)). These data indicated that the chirality-inducing agents in these diamine-forming reactions were chiral phosphoric acids; the acidic additive served as a proton source to neutralize the basic diamine product, helping to release the phosphoric acid/$Rh_2(OAc)_4$ catalyst into the catalytic cycle.

Under the optimized conditions, a wide range of aromatic imines, carbamates, and diazo compounds were evaluated with **5g** as the cocatalyst (Table 2). In most cases, *anti*-diamino acid


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**Table 2.** *anti*-Selective Enantioselective Three-Component Mannich-Type Reactions with 5g[a]

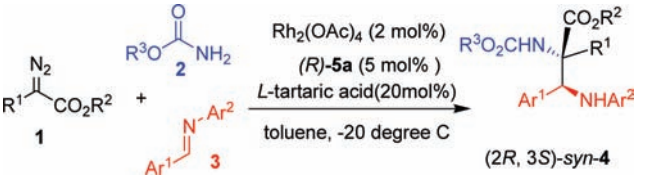

| entry | $R^1/R^2$ | $R^3$ | $Ar^1/Ar^2$ | yield % (anti/syn)[b,c] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | Ph/Me | Bn | Ph/Ph | **4a**, 92 (97:3) | 93 |
| 2 | Ph/Me | $CH_2CCl_3$ | Ph/Ph | **4b**, 77 (97:3) | 93 |
| 3 | Ph/Me | $CMe_3$ | Ph/Ph | **4c**, 81 (93:7) | 87 |
| 4 | *p*-BrPh/Me | Bn | Ph/Ph | **4d**, 89 (97:3) | 90 |
| 5 | *p*-FPh/Me | Bn | Ph/Ph | **4e**, 87 (95:5) | 89 |
| 6 | Ph/Me | Bn | Ph/PMP | **4f**, 85 (96:4) | 90 |
| 7 | Ph/Me | Bn | *m*-Br/PMP | **4g**, 75 (>99:1) | 90 |
| 8 | Ph/Me | Bn | *o*-Br/PMP | **4h**, 66 (97:3) | 92 |
| 9 | Ph/Me | Bn | *p*-BrPh/PMP | **4i**, 76 (98:2) | 94 |
| 10 | *p*-MePh/Me | Bn | *m*-Br/PMP | **4j**, 73 (>99:1) | 93 |
| 11 | *p*-MePh/Me | Bn | *m*-Cl/PMP | **4k**, 72 (99:1) | 95 |
| 12 | Ph/Me | Bn | *p*-BrPh/*p*-ClPh | **4l**, 74 (98:2) | 96 |
| 13 | Ph/Me | Et | Ph/Ph | **4m**, 93 (97:3) | 89 |
| 14 | Ph/Me | Bn | Ph/*p*-BrPh | **4n**, 75 (91:9) | 90 |
| 15[d] | Ph/Me | Bn | Ph/*p*-BrPh | **4n**, 77(**91:9**) | −92 |
| 16 | Ph/Me | Bn | *m*-ClPh/PMP | **4o**, 73 (>99:1) | 93 |
| 17 | Ph/Me | Bn | Ph/*m*-BrPh | **4p**, 70 (96:4) | 89 |
| 18 | Ph/Me | Bn | *p*-$NO_2$/PMP | **4q**, 66 (>99:1) | 90 |
| 19[e] | Bn/Et | Bn | *p*-BrPh/*p*-ClPh | **4r**, 71 (94:6) | 97 |
| 20[e] | Me/Et | Bn | Ph/Ph | **4s**, 88 (75:25) | 99 |

[a] Standard conditions: $Rh_2(OAc)_4$/**5g**/**3**/**2** = 0.004/0.01/0.2/0.26 mmol, with 4 Å MS 100 mg in 5.6 mL of PhMe; 0.26 of mmol **1** in 2.8 mL of PhMe were then added via a syringe pump at −20 °C. [b] Isolated product yield. [c] Determined by chiral HPLC analysis. [d] (*R*)-**5g** (5 mol %) was used to give (2*S*,3*S*)-**4n**. [e] Alkyl-substituted diazoacetates (2 equiv) were used.

esters, *anti*-**4**, were obtained in high yields with excellent stereoselective control (Table 2, entries 1−19). Trichloroethyl carbamate and *tert*-butyl carbamate are equally good partners with regard to yield and stereoselectivities (Table 2, entries 2 and 3). Generally, imines with a halogenated $Ar^1$ gave 10−20% lower yields than did imines with just a phenyl group. It is noteworthy that alkyl-substituted diazoacetates such as ethyl diazophenylpropanate and ethyl diazopropanate were feasible substrates in this reaction, giving the desired products in good to high yields and high to excellent enantioselectivities (entries 19−20).

Remarkably, all substrate combinations (except for alkyl diazo compounds) switched their diastereomeric outcomes, namely from *anti*-selectivity to *syn*-selectivity, when the phosphoric acid catalyst **5g** was replaced by **5a**−**e**. Representative results are tabulated in Table 3. The $Rh_2(OAc)_4$/**5a**-catalyzed three-component coupling reactions of diazo esters, carbamates, and imines delivered *syn*-**4** in good yield, with good to high dr and excellent ee. Thus, by judicious choice of chiral phosphoric acid catalysts, each of the four stereoisomers of the α-substituted α,β-diamino esters could be made at will using the dual catalyst cooperatively

**Table 3.** *syn*-Selective Enantioselective Three-Component Mannich-Type Reactions with Phosphoric Acid 5a[a]




| entry | $R^1/R^2$ | $R^3$ | $Ar^1/Ar^2$ | yield % (*syn*/*anti*)[b,c] | ee %[c] *syn* (*anti*) |
|---|---|---|---|---|---|
| 1 | Ph/Me | Bn | Ph/Ph | **4a**, 90 (90:10) | 96 |
| 2 | *p*-BrPh/Me | Bn | Ph/Ph | **4d**, 79 (85:15) | 93 |
| 3 | *p*-FPh/Me | Bn | Ph/Ph | **4e**, 88 (86:14) | 95 |
| 4 | Ph/Me | Bn | Ph/PMP | **4f**, 78 (75:25) | 95 |
| 5 | *p*-MePh/Me | Bn | *m*-BrPh/PMP | **4j**, 73 (75:25) | >99 |
| 6 | Ph/Me | Et | Ph/Ph | **4m**, 84 (87:13) | 97 |
| 7 | Ph/Me | Bn | Ph/*p*-BrPh | **4n**, 79 (89:11) | 96 |
| 8 | Ph/Me | Bn | Ph/*m*-BrPh | **4p**, 74 (87:13) | 99 |
| 9[d] | Me/Et | Bn | Ph/Ph | **4s**, 67 (35:65) | 88 (76) |

[a] Standard conditions: $Rh_2(OAc)_4$/**5a**/**3**/**2**/**1** = 0.004/0.01/0.2/0.26/0.26 mmol, in 8.4 mL of PhMe, with 4 Å MS 100 mg at −20 °C. [b] Isolated product yield. [c] Determined by chiral HPLC analysis. [d] Alkyl-substituted diazoacetates (2 equiv) were used.

catalyzed three-component ylide trapping protocol. Catalytic asymmetric synthesis of α,β-diamino acid derivatives through carbon−carbon bond-forming reactions represents a particular challenge because it needs both diastereomeric and enantiomeric control of the two newly generated vicinal stereogenic centers in a flexible acyclic molecule. Even though great advances have been made recently in this area,[13] there are limited examples of catalytic synthesis of optically active α,β-diamino acid derivatives with an α-quaternary carbon center.[13g,14] It is worth noting that no efficient method has been documented previously for the synthesis of optically active α-aryl-substituted-α,β-diamino acid derivatives. The current methodology presents an efficient solution toward these challenges providing a novel entry to the biologically important α,β-diamino acid derivatives.[13k,l]

The absolute configurations of *anti*-**4h** (2*R*,3*R*) (from *S*-**5g**) and *syn*-**4n** (2*R*,3*S*) (from *R*-**5a**) were established by X-ray single crystal analysis (see SI); by analogy to *anti*-**4h** and *syn*-**4n**, the stereochemistries of other diamino products were assigned correspondingly. These data also show that, for the use of a chiral phosphoric acid cocatalyst bearing the same absolute configuration, for example (*R*)-**5g** (Table 2, entry 15) and (*R*)-**5a**, the switch of diastereoselectivity in **4** occurred at the quaternary C-2 carbon center.

The exact reasons for the stereoselective control are unclear at the present time and deserve additional detailed study. The proposed transition states in Figure 3 could be used to explain the switch of diastereoselectivity in the presence of different type of PPAs. The *cis*-enolate-like ammonium ylide is proposed due to the intramolecular hydrogen bond.[15] In the PPA cocatalyzed process, the bifunctional PPA could form a larger N−H−OPO−H−N bridge in a proposed transition state **VI**, leading to *syn*-selectivity. In the case of an extremely sterically demanding PPA like **5g**, the restricted PPA space cannot accommodate both the imine and the ylide; thus the open-chain *anti*-TS **VII** may operate, giving rise to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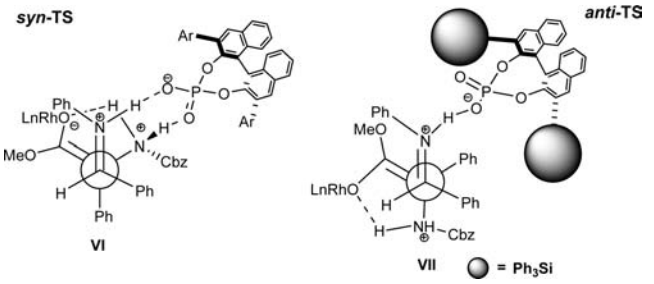


**Figure 3.** Proposed transition states for the switch of diastereoselectivity with different type of PPAs.

the reversal of diastereoselectivity. The fact that the diastereoselectivity switch occurred at the C-2 carbon is in agreement with the proposed models. Though the above models explain the present experimental data, other bridging/nonbridging pathways and the geometry of Z-imines in transition states are also possible.

In summary, by using a dual/cooperative catalysis strategy, the highly reactive protic carbamate ammonium ylides were successfully trapped by imine electrophiles in a controlled manner. These novel diastereoselectively switchable enantioselective three-component reactions open up a superior avenue to all isomers of α, β-diamino acid derivatives with an α-quaternary carbon center in an optically active form. This work demonstrates the strategy of discovering novel multicomponent reactions by irreversible trapping of an active intermediate resulting from two components by a third component. The dual/cooperative catalysis strategy provides an opportunity for controlling the reaction selectivities in the multicomponent reactions, because the appropriate combination of suitable and compatible cocatalysts can affect the intrinsic reaction kinetics in a designed way to activate the desired component selectively. The discovery of more multicomponent reactions using such a strategy is currently in progress in our laboratory.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures, characterization, analysis of enantioselectivities and X-ray crystal structures. This material are available free of charge via the Internet at http://pubs.acs.org.

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