Asymmetric Catalysis

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Dirhodium Carboxylates Catalyzed Enantioselective Coupling Reactions of α-Diazophosphonates, Anilines, and Electron-Deficient Aldehydes**

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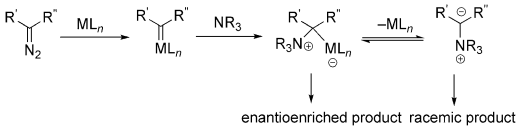
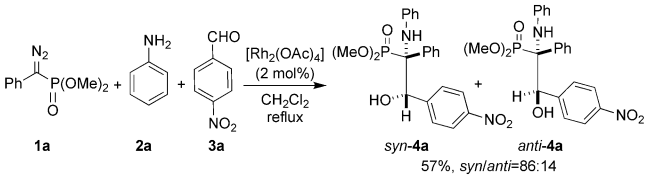
Ammonium ylides are versatile intermediates that are frequently used in the synthesis of complex and diverse nitrogen-containing compounds.[1,2] Transition-metal complexes, including dirhodium(II,II) carboxylates, copper(II) acetylacetonate, and ruthenium(II) porphyrins, are effective catalysts for the generation of ammonium ylides through decomposition of diazo compounds in the presence of amines.[2] While highly enantioselective alkene cyclopropanation,[2,3] carbene X–H (X = C, Si, N, O) insertion,[4–8] and transformation reactions of oxygen ylides[9,10] and sulfur ylides[11] have been achieved by decomposition of diazo compounds in the presence of chiral transition-metal complexes, transition-metal-catalyzed asymmetric reactions of ammonium ylides are rare. The major challenge in developing highly enantioselective metal-catalyzed ammonium ylide reactions is the equilibrium between the metal-bound/stabilized ylide (referred to as metal-bound ylide) and the free ylide; the latter leads to the formation of racemic product (Scheme 1).

In this study, we examined the three-component coupling reaction of α-diazophosphonates, anilines, and electron-deficient aldehydes to give α-amino-β-hydroxyphosphonate compounds (Scheme 2).[12] α-Amino phosphonic acid compounds are key substrates used in the synthesis of phosphonopeptides and could act as enzyme inhibitors, antibiotics, plant growth regulators, and haptens of catalytic antibodies.[13]



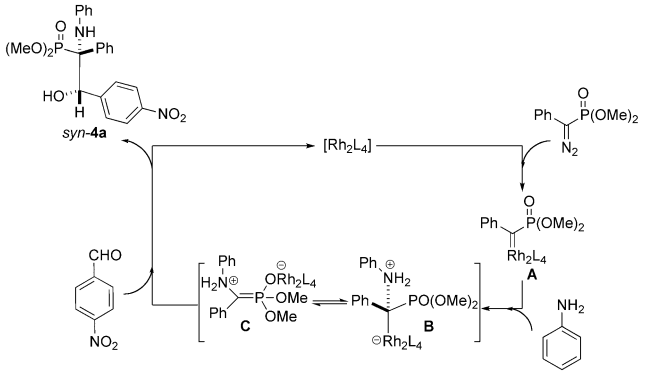
Scheme 1. Ammonium ylide formation by the reaction of metal carbenoid with amine. L = ligand, M = metal.



Scheme 2. Three-component coupling reaction to *syn*-**4a** and *anti*-**4a**.

At the outset, the reaction of dimethyl α-diazo(benzyl) phosphonate **1a**, aniline **2a**, 4-nitrobenzaldehyde **3a**, and [$Rh_2(OAc)_4$] catalyst (2 mol%) in CH_2Cl_2 at 40 °C for 15 hours afforded the two diastereomers *syn*-**4a** and *anti*-**4a** in 57% overall yield and with a *syn*/*anti* ratio of 86:14 (Scheme 2). The structure of the major isomer *syn*-**4a** was determined by X-ray crystallography (see the Supporting Information).

A proposed mechanism for this Rh-catalyzed three-component reaction is shown in Scheme 3. With reference to previous work on Brønsted acid/[$Rh_2(OAc)_4$]-catalyzed coupling reaction of diazoester, carbamate, and imine,[14c] the rhodium catalyst decomposes α-diazophosphonate to generate Rh–carbene species **A**, which is trapped by aniline to give



Scheme 3. Proposed mechanism for the three-component coupling reaction.

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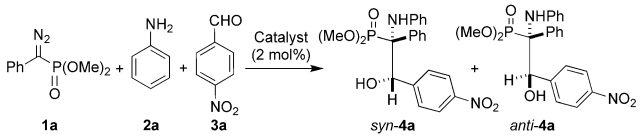
metal-bound ammonium ylide intermediate **B**/**C**. Subsequent nucleophilic addition of the intermediate to the aldehyde gives the α-amino-β-hydroxyphosphonate.

To examine the significance of metal-bound ylide intermediate **B**/**C** in the reaction, we performed DFT calculations using B3LYP functionals to examine the addition of ylide intermediate **B**/**C** to the aldehyde in the three-component reaction of **1a**, **2a**, and **3a** catalyzed by $[Rh_2(O_2CH)_4]$. The computed free-energy surface is shown in Scheme 4. The formation of **C** from **B** is endergonic by 12.8 kcal mol^{-1}, but the subsequent nucleophilic addition of **C** to the aldehyde via **D** is relatively facile, requiring an activation free energy of 3.7 kcal mol^{-1}. In contrast, the pathway via the free ylide has an overall activation free energy of 20.8 kcal mol^{-1} via TS_{F-G}, which is 4.7 kcal mol^{-1} higher than that for the pathway via **C** (16.1 kcal mol^{-1}). Our effort to locate the transition state of the direct addition of **B** to the aldehyde was unsuccessful. These results show that addition of metal-bound intermediate **C** to the aldehyde is the reaction pathway with the lowest energy. We anticipated that chirality transfer would occur in this pathway via the metal-bound ylide if a chiral dirhodium(II,II) catalyst was used.

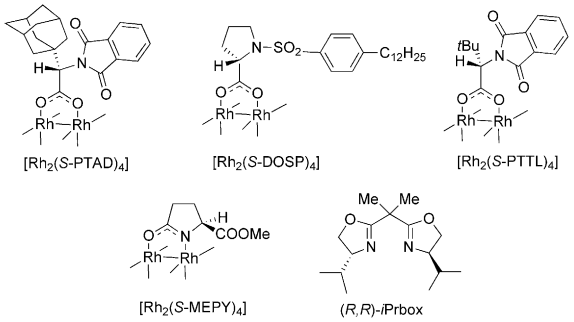
To validate our hypothesis, a series of chiral dirhodium(II,II) carboxylates and the Cu^{I} complex of (*R*,*R*)-*i*Prbox, which have been reported to give excellent enantioselectivity in alkene cyclopropanation and carbene C–H insertion reactions, were examined for the three-component coupling reaction of **1a**, **2a**, and **3a** (Table 1). With $[Rh_2(S\text{-PTAD})_4]$[15] as catalyst, **4a** was obtained in 73% yield with a *syn*/*anti* ratio of 80:20 and an *ee* value of 77% (Table 1, entry 1). $[Rh_2(S\text{-DOSP})_4]$[16] and $[Rh_2(S\text{-PTTL})_4]$[17] gave *syn*-**4a** with 22% and 68% *ee*, respectively (Table 1, entries 2 and 3). $[Rh_2(S\text{-MEPY})_4]$[18] failed to catalyze this reaction (Table 1, entry 4). When CuOTf/(*R*,*R*)-*i*Prbox was used, both product yield and enantioselectivity were low (Table 1, entry 5). With $[Rh_2(S\text{-PTAD})_4]$ as catalyst, CH_2Cl_2 was the best solvent (Table 1, entries 1, 6, and 7). Lowering the reaction temperature to room temperature resulted in a long reaction time (40 h) and lower product yield and enantioselectivity (Table 1, entry 8). Increasing the reaction temperature to 85 °C led to reduction of both the product yield and enantioselectivity (Table 1, entry 9).

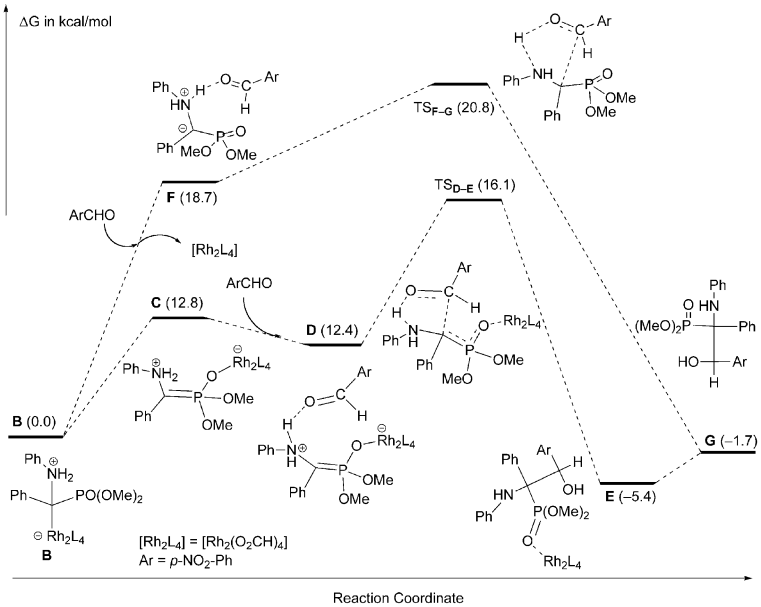
Table 1: Catalyst screening and optimization of the coupling reaction of **1a**, **2a**, and **3a**.[a]



Entry	Catalyst	Solvent	*T* [°C]	Yield[b] [%]	*syn*/*anti*[c]	*ee* (*syn*) [%][d]
1	$[Rh_2(S\text{-PTAD})_4]$	CH_2Cl_2	40	73	80:20	77
2	$[Rh_2(S\text{-DOSP})_4]$	CH_2Cl_2	40	54	84:16	22
3	$[Rh_2(S\text{-PTTL})_4]$	CH_2Cl_2	40	65	81:19	68
4	$[Rh_2(S\text{-MEPY})_4]$	CH_2Cl_2	40	n.r.	–	–
5	CuOTf/ (*R*,*R*)-*i*Pr-box	CH_2Cl_2	40	32	90:10	9
6	$[Rh_2(S\text{-PTAD})_4]$	toluene	40	35	62:38	27
7	$[Rh_2(S\text{-PTAD})_4]$	DMB	40	n.r.	–	–
8[e]	$[Rh_2(S\text{-PTAD})_4]$	CH_2Cl_2	25	54	85:15	64
9	$[Rh_2(S\text{-PTAD})_4]$	$(CH_2Cl)_2$	85	30	66:34	42

[a] **1a**:**2a**:**3a**:catalyst = 1:1.5:3:0.02, reaction time = 12–15 h. [b] Yields of isolated products. [c] Ratio of *syn*/*anti* determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction time was 40 h. DMB = 2,2-dimethylbutane; n.r. = no reaction; OTf = trifluoromethanesulfonate.



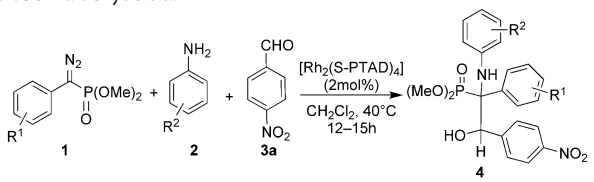


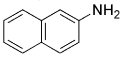
Scheme 4. Computed free-energy surface for the coupling reaction.

The scope of $[Rh_2(S\text{-PTAD})_4]$-catalyzed three-component coupling reactions of derivatives **1** of dimethyl α-diazo(benzyl)phosphonate, anilines **2**, and 4-nitrobenzaldehyde **3a** was examined with the optimized conditions (Table 2). Bulky *ortho* substituent(s) on aniline significantly improved the enantioselectivity up to 98% and diastereoselectivity up to 90:10 (Table 2, entries 1–5). Substitution at the *meta* position has a slight impact on both the enantioselectivity and diastereoselectivity (Table 2, entries 6–7). When 4-chloroaniline **2i** was used, product **4i** was obtained in 91% *ee* (Table 2, entry 8).

The effect of substitution on the benzyl group of diazo compound **1** was examined by using 2-

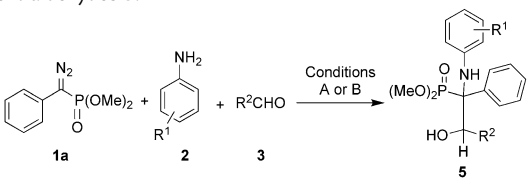
Table 2: Scope of enantioselective three-component coupling reaction of derivatives **1** of dimethyl α-diazo(benzyl)phosphonate, anilines **2**, and 4-nitrobenzaldehyde **3a**.[a]

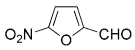
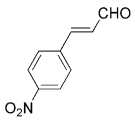


Entry	**1**	R^1	**2**	R^2	**4**, Yield [%][b]	*syn*/*anti*[c]	*ee* (*syn*) [%][d]
1	**1a**	H	**2b**	2-Me	**4b**, 80	89:11	96
2	**1a**	H	**2c**	2-Br	**4c**, 85	90:10	98
3	**1a**	H	**2d**	2-Cl	**4d**, 81	83:17	89
4	**1a**	H	**2e**:		**4e**, 82	89:11	94
5	**1a**	H	**2f**	2-Br, 4-Cl	**4f**, 86	86:14	95
6	**1a**	H	**2g**:		**4g**, 69	78:22	74
7	**1a**	H	**2h**	3-Cl	**4h**, 75	81:19	73
8	**1a**	H	**2i**	4-Cl	**4i**, 78	90:10	91
9	**1a**	H	**2j**	3-OMe	**4j**, 56	76:24	60
10	**1b**	4-Cl	**2b**	2-Me	**4k**, 78	84:16	89
11	**1c**	4-Me	**2b**	2-Me	**4l**, 78	88:12	97
12	**1d**	4-OMe	**2b**	2-Me	**4m**, 56	87:13	71
13	**1b**	4-Cl	**2e**:		**4n**, 80	87:13	94
14	**1c**	4-Me	**2k**	2-F	**4o**, 83	82:18	79
15	**1c**	4-Me	**2l**	2-Br, 4-F	**4p**, 82	80:20	93

[a] **1**:**2**:**3a**:catalyst = 1:1.5:3:0.02. [b] Yields of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase.

Table 3: Scope of enantioselective three-component coupling reaction of dimethyl α-diazo(benzyl)phosphonate **1a**, anilines **2**, and electron-deficient aldehydes **3**.[a]



Entry	**2**	**3**	R^2	**5**, Yield [%][b]	*syn*/*anti*[c]	*ee* (*syn*) [%][d]
1[e]	**2c**	**3b**	4-CO_2Me	**5a**, 77	91:9	66
2[f]				**5a**, 79	87:13	79
3[e]	**2c**	**3c**	4-NO_2	**5b**, 69[h]	89:11	67
4[f]				**5b**, 77	88:12	86
5[g]	**2c**	**3d**:		**5c**, 64	87:13	77
6[f]				**5c**, 65	85:15	75
7[e]	**2c**	**3e**:		**5d**, 0		
8[f]				**5d**, 83[i]	94:6	80
9[e]	**2b**	**3b**	4-CO_2Me	**5e**, 69	90:10	61
10[f]				**5e**, 75	88:12	79
11[e]	**2b**	**3c**	4-NO_2	**5f**, 71[j]	85:15	75
12[f]				**5f**, 74	83:17	79

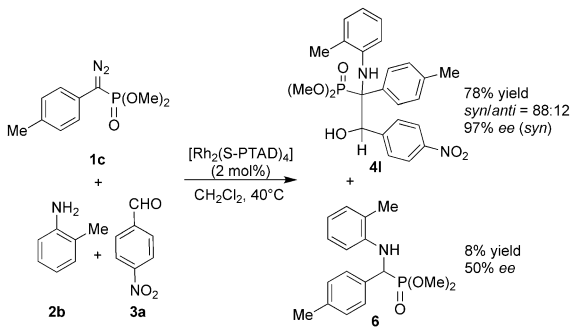
Conditions A: [Rh_2(S-PTAD)$_4$] (2 mol%), CH_2Cl_2, 40°C, 24 h. Conditions B: [Rh_2(S-PTTL)$_4$] (2 mol%), CH_2Cl_2, 40°C, 12–15 h. [a] **1a**:**2**:**3**:catalyst = 1:1.5:3:0.02. [b] Yields of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. [e] Conditions A. [f] Conditions B. [g] Conditions A with reaction time of 15 h. [h] Yield of isolated product based on substrate conversion of 90%. [i] Yield of isolated product based on substrate conversion of 75%. [j] Yield of isolated product based on substrate conversion of 85%.

methylaniline **2b** or 4-aminoindane **2e** as substrate. Both Cl and Me substituents led to high *ee* values (89–97%, entries 10, 11, and 13). However, with the OMe substituent, the enantioselectivity decreased to 71% *ee* (Table 2, entry 12). The reaction of **1c**, **3a**, and 2-fluoroaniline **2k** (Table 2, entry 14) gave comparable enantioselectivity (79% *ee*) to that obtained for the reaction of **1a**, **3a**, and **2a** (Table 1, entry 1). Presumably, the steric effect of an 2-F substituent of aniline is not large. This suggestion is supported by the reaction of **1c**, **3a**, and 4-fluoro-2-bromoaniline **2l**, affording the corresponding product **4p** in 93% *ee* (Table 2, entry 15). Changing **1a** to diethyl α-diazo(benzyl)phosphonate led to corresponding product in 74% yield with 79:21 d.r. and 57% *ee*. The absolute configuration of *syn*-**4l** was determined to be 2*S*,3*S* by X-ray crystallography using anomalous dispersion effects in diffraction measurements on the crystal (see Figure S2 in the Supporting Information).

We next extended the scope of aldehydes for this three-component reaction (Table 3, entries 1–8). Various electron-deficient aldehydes underwent the three-component reaction with [Rh_2(*S*-PTAD)$_4$] or [Rh_2(*S*-PTTL)$_4$] as catalyst to give the corresponding products in 64–83% yield with 85:15–94:6 d.r. and 66–86% *ee*. With [Rh_2(*S*-PTAD)$_4$] as catalyst, 4-carbomethoxybenzaldehyde **3b** was less reactive than **3a**, requiring a reaction time of 24 hours and giving the corresponding product in 77% yield and 66% *ee* (Table 3, entry 1). When the less sterically encumbered [Rh_2(*S*-PTTL)$_4$] was used as catalyst, the reaction was completed in 15 hours and led to slightly higher product yield and enantioselectivity (79% *ee*, Table 3, entry 2). Similar results were obtained for the reaction of **1a**, **2c**, and 3-nitrobenzaldehyde **3c** (Table 3, entries 3 and 4). When heteroaromatic aldehyde **3d** was used, catalysis with [Rh_2(*S*-PTAD)$_4$] and [Rh_2(*S*-PTTL)$_4$] led to **5c** in 64% and 65% yields and with 77% *ee* and 75% *ee*, respectively (Table 3, entries 5 and 6). The vinyl aldehyde **3e** was reactive and gave **5d** in 83% yield and with 80% *ee* when [Rh_2(*S*-PTTL)$_4$] was used as catalyst, but failed to give **5d** when [Rh_2(*S*-PTAD)$_4$] was used instead (Table 3, entries 7 and 8). Similarly, the reactions of 2-methylaniline **2b**, **1a**, and aldehyde **3b** or **3c** gave comparable results to that obtained for the similar reaction with 2-bromoaniline **2c** (Table 3, entries 9–12).

In all of the entries depicted in Tables 2 and 3, the products of carbene N–H insertion of anilines were detected

in 2–10% yields. The N–H insertion product **6** formed in the reaction of **1c**, **2b**, and **3a** (Scheme 5, Table 2, entry 11) was isolated in 8% yield and in 50% *ee* in contrast to 97% *ee* of



Scheme 5. Formation of three-component coupling product **4l** versus N–H insertion product **6**.

the corresponding three-component coupling product *syn*-**4l**. This result suggests that the metal-bound ylide intermediate **B**/**C** may not be the sole species responsible for the carbene N–H insertion of anilines. Recent studies showed that transition-metal-catalyzed carbene insertion into the N–H bond of amines could be a stepwise process that involves initial ammonium ylide formation followed by [1,2]-proton shift.[6d,8,14]

In summary, we have developed a highly enantioselective metal-catalyzed three-component coupling reaction of α-diazophosphonates, anilines, and electron-deficient aldehydes. By using the chiral rhodium catalysts $[Rh_2(S\text{-PTAD})_4]$ or $[Rh_2(S\text{-PTTL})_4]$, a series of α-amino-β-hydroxyphosphonates were obtained in good to high yields and with good to high enantioselectivities. The high level of enantiocontrol provides evidence for the intermediacy of a metal-bound ammonium ylide in the nucleophilic addition step.

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