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Synergistic Rhodium(II) Carboxylate and Brønsted Acid Catalyzed Multicomponent Reactions of Enalcarbenoids: Direct Synthesis of α-Pyrrolylbenzylamines

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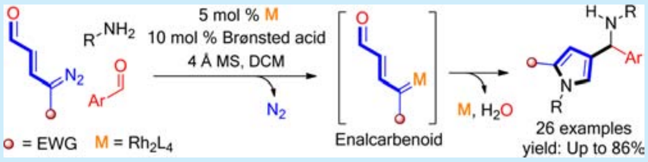
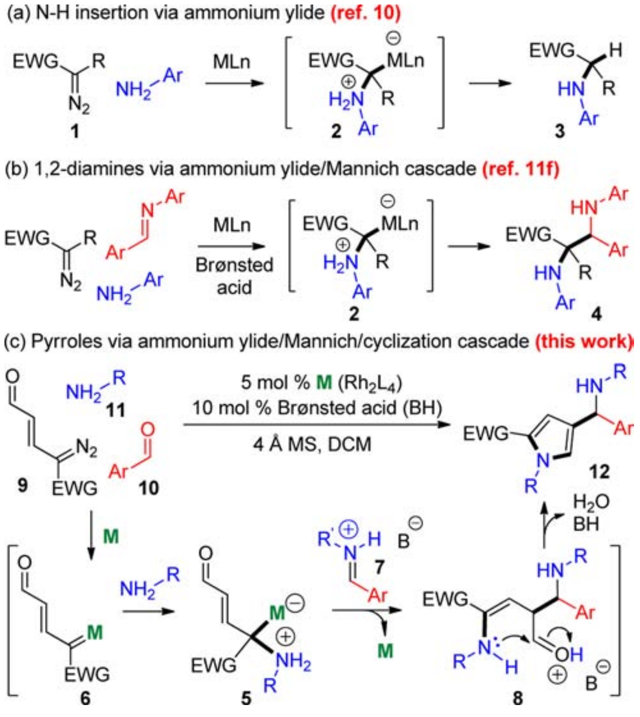
Ⓢ *Supporting Information*



ABSTRACT: The design of a synergistic rhodium(II) carboxylate and BINOL phosphoric acid catalyzed efficient multicomponent reaction of enaldiazo compounds, arylamines, and aryl aldehydes leading to the first transition-metal-catalyzed direct synthesis of valuable α-pyrrolylbenzylamines is disclosed. The reaction is proposed to involve a transient ammonium ylide of a new class of electrophilic rhodium enalcarbenoid, its regioselective Mannich reaction, and a cyclocondensation cascade. The methodology was used in a highly diastereoselective synthesis of a binaphthyl based chiral pyrrole.

Pyrroles are an important class of heterocyclic compounds manifested in various natural products, fine chemicals, pharmaceuticals, materials, and catalysts.[1−3] Hence, development of new methodologies toward functionalized pyrroles continues to be an active research area.[4−6] Classical methodologies include Paal−Knorr, Knorr, and Hantzsch syntheses. The majority of recent methodologies are focused on transition-metal-catalyzed isomerizations and annulations.[6] Remarkably, these methodologies offer efficient construction of polysubstituted pyrroles with diverse substitution patterns, regioselectivity, and atom economy. However, despite these advances, the direct construction of chiral pyrroles by transition-metal-catalyzed methodologies have remained unexplored. The conventional approaches for chiral pyrroles involve enantioselective functionalization of the pyrrole moiety, which offers limited scope.[7] Thus, the development of new methodologies, in particular those involving transition-metal-catalyzed direct construction of functionalized chiral pyrroles would be synthetically highly valuable.

Scheme 1. N−H Insertion and Multicomponent Reactions via Protic Ammonium Ylides


(a) N-H insertion via ammonium ylide (ref. 10)

(b) 1,2-diamines via ammonium ylide/Mannich cascade (ref. 11f)

(c) Pyrroles via ammonium ylide/Mannich/cyclization cascade (this work)

Transition metal catalyzed insertion of X−H (X = N, O, S, B, Si) bonds into stabilized diazo compounds has evolved as a powerful strategy for rapid access to valuable heteroatom containing molecules.[8−11] In particular, N−H insertion has been very useful in delivering biologically important α-amino acids, α-aminophosphonates and heterocyclic compounds.[10] It has been proposed that N−H insertion into diazo compound **1** proceeds through an initial high energy protic ammonium ylide **2** formation followed by 1,2-proton transfer leading to amine derivative **3** (Scheme 1a).[10] Recently, the Hu and Che groups have successfully developed elegant multicomponent reactions by trapping protic ammonium ylides **2** (M = Rh_2L_4) with various electrophiles, including imines (Scheme 1b), aldehydes, and enones leading to synthetically valuable 1,2-diamines **4**, 1,2-aminols, and pyrrolidine derivatives, respectively.[11] We envisioned that the protic ammonium ylides **5** (Scheme 1c) derived from our recently designed rhodium enalcarbenoids **6**[12] would offer (a) stabilization due to the extended conjugation and (b) concomitant vinylogous nucleophilicity toward electrophiles such as iminium species **7**, leading to Mannich product **8** with new stereogenic centers. These key features of enalcarbenoids **6**

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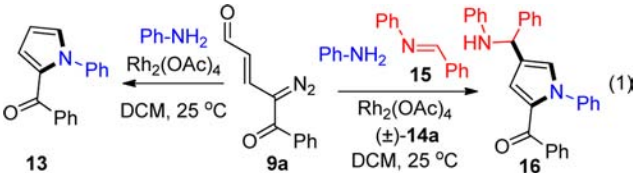
have the potential to offer distinct new classes of cascade reactions for rapid synthesis of nitrogen containing chiral molecules. Herein, we disclose the design of an efficient multicomponent reaction, cooperatively catalyzed by rhodium(II) carbxylate and BINOL phosphoric acid, involving enaldiazo compound **9**,[12] aryl aldehyde **10**, and amine **11** (R= Ar, Boc) leading to the direct synthesis of *α*-(3-pyrrolyl)benzylamines **12** consisting of a new stereogenic center (Scheme 1c).

Our studies began with the reaction of diazoenal **9a** with aniline in the presence of a catalytic amount of $Rh_2(OAc)_4$ (eq 1).

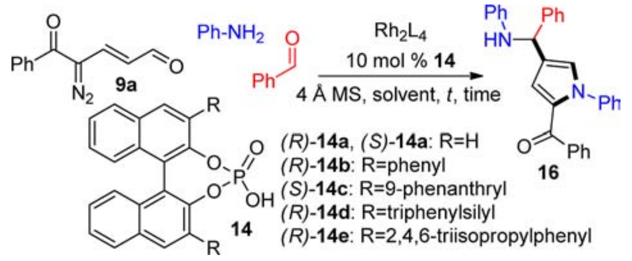


When a solution of diazoenal **9a** (0.15 mmol, 1 equiv) in dichloromethane (DCM, 2 mL) was added slowly over 2 h to a solution of aniline (0.15 mmol) and 2 mol % of $Rh_2(OAc)_4$ in DCM (1 mL) at 10 °C, pyrrole **13** was obtained in 10% yield, presumably via ammonium ylide/cyclocondensation cascade. The yield was improved to 63% when the same reaction was carried at 25 °C.

Encouraged by this result, we next turned our attention to testing the hypothesis of capturing the transient ammonium ylide **5** (EWG = benzoyl) with an imine electrophile **15**. Gratifyingly, when a solution of **9a** (0.14 mmol, in 2 mL of DCM) was added slowly over 2 h to a mixture of aniline (0.14 mmol), imine **15** (0.14 mmol), 2 mol % of $Rh_2(OAc)_4$, and 10 mol % of (±)-BINOL phosphoric acid **14a** in DCM (2 mL) at 25 °C, the *α*-(3-pyrrolyl)benzylamine **16** possessing a new stereogenic center was formed in 58% yield (eq 1).[13] It is noteworthy that the Mannich reaction proceeded with complete regioselectivity, which further promoted the subsequent cyclocondensation step resulting in [4 + 1]-pyrrolannulation of the multicomponent reaction (Scheme 1c). In the absence of **14a**, only a trace amount of **16** was formed along with pyrrole **13**. In a separate experiment, when pyrrole **13** was treated with imine **15** (1 equiv), 10 mol % of Bronsted acid (±)-**14a**, and 2 mol % of $Rh_2(OAc)_4$ in DCM, the desired product **16** was not formed even after prolonged reaction time (6 h) at 25 °C. This experiment revealed that the imine electrophile **15** was captured before the cyclocondensation step to form pyrrole ring in **16**.[13] Other Brønsted acids like benzoic acid, camphorsulfonic acid, *p*-toluenesulfonic acid, and trifluoroacetic acid did not give desired product **16**.

To further simplify the reaction, we were curious to know if the imine **15** can be generated in situ. Delightfully, when diazoenal **9a** (1 equiv, 0.14 mmol in 2 mL of DCM) was added slowly to a mixture of aniline and benzaldehyde (0.28 mmol:0.14 mmol in 2 mL of DCM, prestirred for 1 h in the presence of 4 Å MS), 10 mol % of **14a**, and 2 mol % of $Rh_2(OAc)_4$, the desired pyrrole **16** was obtained in 53% yield. As shown in Table 1, further optimization studies revealed that low Rh(II) catalyst loading leads to diminished yields (45%, entry 2). However, increasing the catalyst loading to 5 mol % improved the yield (62%, entry 3). At this stage, we decided to test the role of temperature on the efficiency of the catalytic process. At lower temperature, the reaction was sluggish and incomplete even after longer reaction time (entry 4). High temperature gave diminished yield (48%, entry 5) due to fast decomposition of the diazo substrate. Consistent and better yields were obtained at 10 °C (79%, entry 6).

Table 1. Optimization Studies[a,13]



entry	Rh_2L_4 (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Rh_2(OAc)_4$(2)	CH_2Cl_2	25	2	53
2	$Rh_2(OAc)_4$(1)	CH_2Cl_2	25	2	45
3	$Rh_2(OAc)_4$(5)	CH_2Cl_2	25	2	62
4	$Rh_2(OAc)_4$(5)	CH_2Cl_2	0	10	42
5	$Rh_2(OAc)_4$(5)	CH_2Cl_2	45	2	48
6[c]	**$Rh_2(OAc)_4$(5)**	**CH_2Cl_2**	**10**	**2**	**79**
7[d]	$Rh_2(OAc)_4$(5)	CH_2Cl_2	10	2	45
8	$Rh_2(OAc)_4$(5)	$CHCl_3$	10	2	74
9	$Rh_2(OAc)_4$(5)	$C_2H_4Cl_2$	10	2	75
10	$Rh_2(OAc)_4$(5)	toluene	10	2	61
11	$Rh_2(Oct)_4$(5)	CH_2Cl_2	10	2	72
12	$Rh_2(esp)_4$(5)	CH_2Cl_2	10	2	69
13	$Rh_2(TFA)_4$(5)	CH_2Cl_2	10	2	56
14	$Rh_2(R\text{-DOSP})_4$(5)	CH_2Cl_2	10	2	71
15	$Rh_2(S\text{-DOSP})_4$(5)	CH_2Cl_2	10	2	68
16	$Rh_2(R\text{-PTAD})_4$(5)	CH_2Cl_2	10	2	64
17[e]	$Rh_2(OAc)_4$(5)	CH_2Cl_2	10	2	51
18[f]	$Rh_2(OAc)_4$(5)	CH_2Cl_2	10	2	56
19[g]	$Rh_2(OAc)_4$(5)	CH_2Cl_2	10	2	56
20[h]	$Rh_2(OAc)_4$(5)	CH_2Cl_2	10	2	52

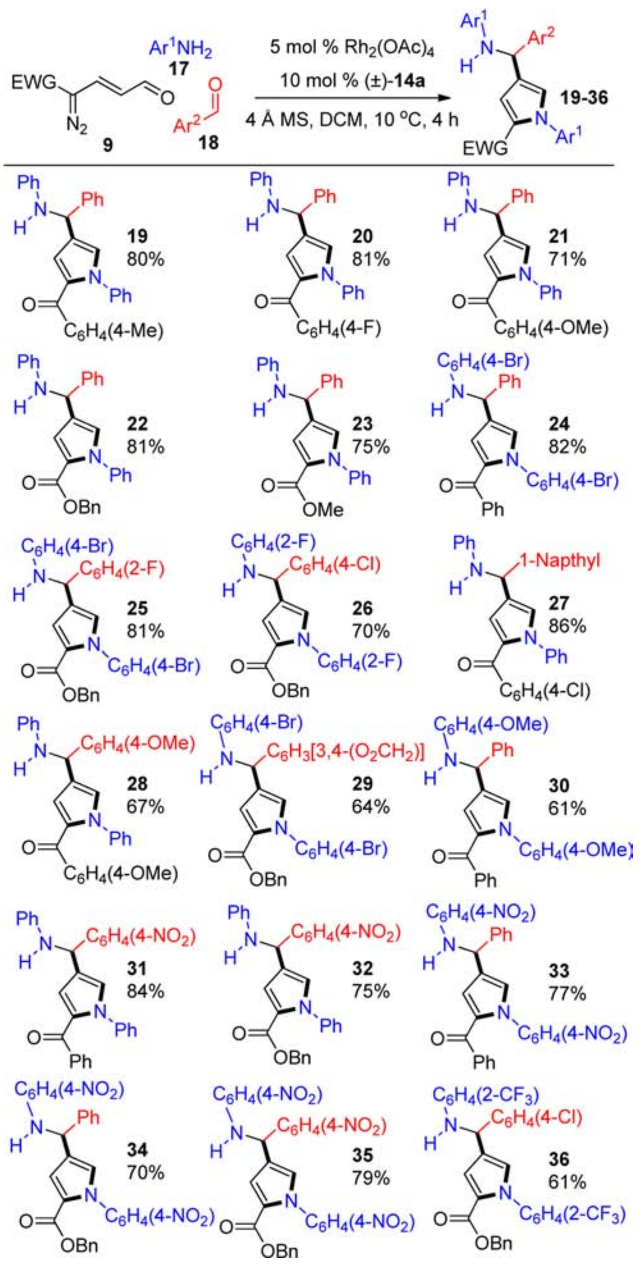
[a] Conditions: aniline/benzaldehyde/**9a** = 0.28:0.14:0.17 mmol. (*R*)-**14a** was used for entries 1–16. [b] Isolated yields. [c] Same yield obtained with (±)-**14a**. [d] 5 mol % of (*R*)-**14a** was used. [e] (*R*)-**14b** was used. [f] (*S*)-**14c** was used. [g] (*R*)-**14d** was used. [h] (*R*)-**14e** was used.

Use of 5 mol % of (±)-**14a** gave reduced yield (45%, entry 7). Among the solvents, halogenated solvents gave clean reactions and good yields (entries 8 and 9) compared to nonpolar solvent (entry 10). With respect to catalyst screening, various other Rh(II) carboxylates promoted the reaction (entry 11–16). However, $Rh_2(OAc)_4$ proved to be a catalyst of choice in terms of efficiency and cost. Interestingly, the reaction gave only <10% ee for pyrrole **16** despite the use of various chiral phosphoric acids **14** (entry 14–16) and chiral rhodium(II) carboxylate catalysts (entry 17–20).

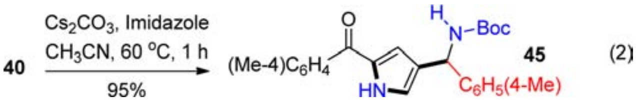
With the optimized conditions in hand, the generality of the reaction was tested with various diazoenals **9**, anilines **17**, and aryl aldehydes **18** (Scheme 2). Both keto-diazoenals and ester-diazoenals gave excellent yields of pyrroles **19**–**23** (71–81%) with aniline and benzaldehyde. The halo-substituted anilines and aryl aldehydes also gave very good yields of pyrroles **24**–**26** (70–82%). However, the electron-rich aryl aldehydes and anilines gave diminished yields of pyrroles **28**–**30** (61–67%), presumably due to the slow rate of Mannich reaction. On the other hand, electron-deficient anilines and aryl aldehydes gave high yields of pyrroles **31**–**35** (70–84%). The reaction was sensitive to steric environment in anilines. The hindered 2-(trifluoromethyl)-aniline gave a low yield of pyrrole **36** (61%), whereas 2,4,6-trimethylaniline did not give the desired pyrrole.

The generality of the methodology was further tested with versatile Boc-carbamates **37** and preformed Boc-imines **38** of aryl aldehydes (Scheme 3). To our delight, both keto- and ester-diazoenals smoothly participated in the multicomponent

Scheme 2. Multicomponent [4 + 1] Pyrrolannulation with Anilines[13]



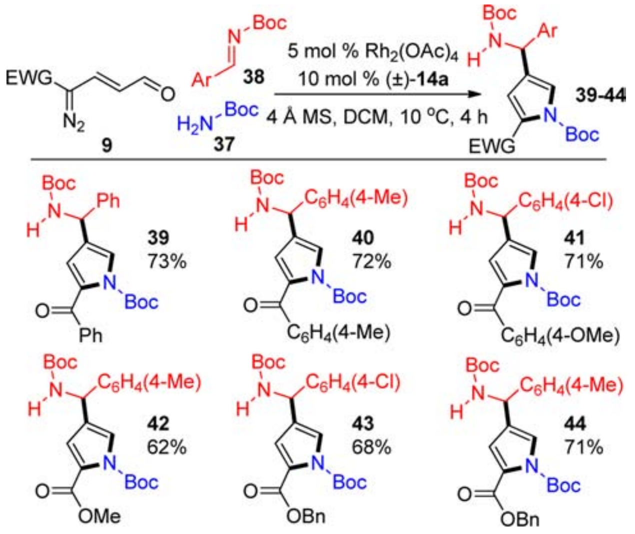
reaction to deliver densely functionalized *N*-Boc-pyrrolylamines **39–44** in 62–73% yield. The *N*-Boc-pyrrole **40** was conveniently deprotected to N–H pyrrole **45** in high yield (eq 2).



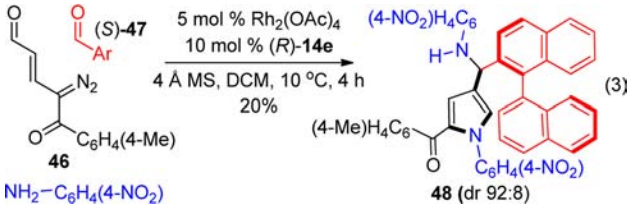
(2)

To probe the role of chiral aryl aldehyde on establishing the proximal chiral center in the Mannich step, the multicomponent reaction was carried with keto-diazoenal **46**, 4-nitroaniline, and chiral binaphthyl aldehyde (*S*)-**47** (eq 3). Although the sterically crowded environment on **47** retarded the reaction, it played a critical role on the diastereoselectivity of the chiralpyrrole product **48**. The best diastereoselectivity (92:8) was obtained with sterically crowded BINOL phosphoric acid (*R*)-**14e**.[13]

Scheme 3. Multicomponent [4 + 1]-Pyrrolannulation with *N*-Boc-carbamates[a,b,13]



[a]Conditions: **37**:**38**:**9** = 0.13:0.13:0.16 mmol. [b]Isolated yields.



(3)

In summary, we have designed a highly efficient multicomponent reaction of diazoenals, arylamines, and aryl aldehydes cooperatively catalyzed by rhodium(II) carboxylate and BINOL-phosphoric acid for the first direct synthesis of valuable *α*-(3-pyrrolyl)benzylamines with a new stereogenic center. The reaction is proposed to involve formation of a transient protic ammonium ylide from the rhodium enalcarbenoid, a regioselective Mannich reaction and a cyclocondensation cascade. The methodology was used in the efficient synthesis of versatile *N*-Boc-pyrroles and a highly diastereoselctive synthesis of binaphthyl-based chiral pyrrole. Further studies are ongoing toward the mechanistic aspects of this novel multicomponent reaction and its application to the natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and X-ray crystal structure data of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated with respect and affection to Professor Goverdhan Mehta on his 71st birthday.

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(13) See the Supporting Information for experimental details, mechanistic study, and characterization.