Multicomponent Reactions

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Diversity-Oriented Three-Component Reactions of Diazo Compounds with Anilines and 4-Oxo-Enoates**

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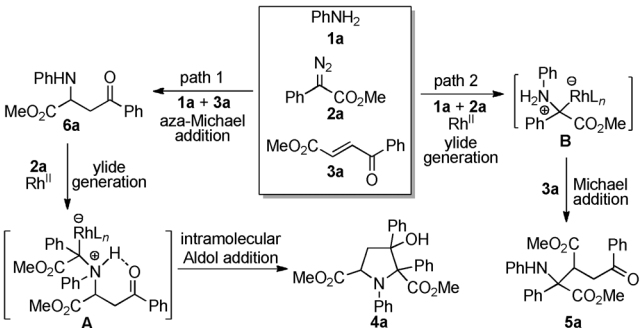
Diversity-oriented synthesis (DOS) has emerged as an important area in the disciplines of medicinal chemistry and chemical biology.[1] The central goal of DOS is to provide molecules containing maximum complexities and structural diversities in the minimum number of synthetic steps to meet the high demand of biological evaluations. Within this context, multicomponent reactions (MCRs) offer significant advantages over traditional chemical synthesis owing to their atom- and step-economy, as well as their high synthetic efficiency in generating molecular diversity through structural modulations of each component participating in the reactions.[1e,f,2] However, most MCRs can only proceed by one sequential pathway leading to only one type of product skeleton.[2] Because of the substrate compatibility and adaptability of the substrates to reaction conditions, MCRs which involve more than one type of reaction pathway starting from the same participants have remained unexplored.[3] Toward this end, herein, we report a $[Rh_2(OAc)_4]$-catalyzed three-component reaction of diazo compounds with anilines and 4-oxo-enoates which can lead to divergent product patterns through a switch in the reaction pathway.

As part of our research efforts aimed at the development of new MCRs through electrophilic trapping of active ammonium ylide intermediates generated from metal carbenoids,[3–6] we chose 4-oxo-enoate as a new type of electrophile for the trapping of an ammonium ylide by Michael addition. Following similar mechanistic considerations proposed in our previously developed three-component reactions, we envisioned that in the presence of the $[Rh_2(OAc)_4]$ catalyst, the proposed transformation between the diazo compound **2a**, aniline **1a**, and the 4-oxo-enoate **3a** should proceed through ylide generation/Michael addition to provide the α-amino-ester-derived product **5a** (Scheme 1, path 2). Indeed, as the reaction went to completion,[7] the desired product **5a** was detected. However, a certain amount of the aza-Michael addition product **6a** from **1a** and **3a**,[8] as well as a new type of pyrrolidine product **4a** were all detected in the reaction system.[9] The pyrrolidine **4a** should come from **6a** through an ylide generation/intramolecular aldol addition pathway (Scheme 1, path 1). The unexpected formation of **4a** is quite novel since it is the first time that an ammonium ylide generated from a secondary amine is trapped by a relatively inactive ketone carbonyl group. The complex reaction pathways in this three-component system make it very difficult to achieve efficient pathway control. However, if such controls could be efficiently utilized, it would become an ideal platform for divergent synthesis of different types of products starting from the same reactants. Since the key issue of pathway control lies in the generation of either **5a** or **6a** from competing reactions between either a metal carbenoid or **3a** with aniline **1a**, we envisioned that a change in the addition sequence of reactants could control the reaction pathways and therefore overcome the competition problem, and thus exclusively lead to either of desired products.



Scheme 1. Possible reaction pathways between aniline (**1a**), phenyl diazoacetate (**2a**), and the 4-oxo-enoate **3a** in the presence of $[Rh_2(OAc)_4]$.

In view of the novelty and challenge of the aza-Michael addition/ylide generation/intramolecular aldol addition pathway leading to pyrrolidine-derived products (Scheme 1, path 1),[10] which are important biologically active molecules, we turned our initial attention to optimization of reaction conditions for the exclusive generation of **4a**. First of all, to validate the proposed pathway for the production of **4a**, **6a** was prepared and reacted with **2a** in the presence of 1 mol% $[Rh_2(OAc)_4]$, and **4a** was obtained in 96% yield with a 82:18 diastereomeric ratio (Scheme 2). This result confirmed our hypothesis about the reaction pathway. In contrast, since the formation of **4a** from **6a** under rhodium(II)-catalyzed conditions was very efficient, the key issue for the proposed overall three-component reaction should lie in the complete formation of **6a** from **1a** and **3a**. Toward this end, to achieve complete formation of **6a** and to avoid the unwanted formation of the ylide intermediate **B**, **1a** and **3a** were reacted for 1 hour in the presence of 4 Å molecular sieves before the addition of $[Rh_2(OAc)_4]$ and **2a** (Table 1, entry 1).

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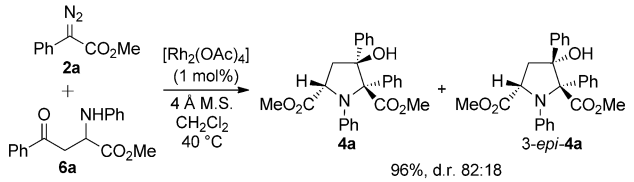
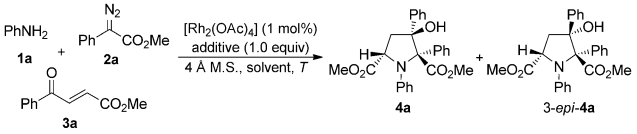


Scheme 2. Reaction between **6a** and **2a** in the presence of $[Rh_2(OAc)_4]$ to afford **4a**. M.S. = molecular sieves.

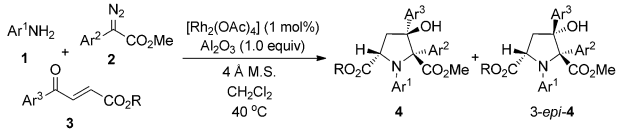
Table 1: Optimization of the reaction conditions for the aza-Michael addition/ylide generation/intramolecular aldol addition pathway.[a]



Entry	Additive	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]
1	–	toluene	40	24	82:18
2	Al_2O_3	toluene	40	66	87:13
3	Al_2O_3	CH_2Cl_2	40	77	92:8
4[d]	Al_2O_3	CH_2Cl_2	40	78	93:7
5[d,e]	Al_2O_3	CH_2Cl_2	40	83	93:7
6[d–f]	Al_2O_3	CH_2Cl_2	40	88	93:7

[a] Unless otherwise noted, the reaction was carried out on a 0.10 mmol scale (**1a**/**2a**/**3a** = 1.0:1.4:1.1). A mixture of **1a**, **3a**, 4 Å M.S. (100 mg), and Al_2O_3 (alkaline, 200–300 mesh) in 0.5 mL of the solvent was stirred for 1 h before $[Rh_2(OAc)_4]$ was added, then **2a** in 0.5 mL of the solvent was added by syringe pump over 1 h. [b] Combined yield of the isolated **4a** and 3-*epi*-**4a**. [c] The d.r. value of **4a**/3-*epi*-**4a** was determined by HPLC. [d] Al_2O_3 (activated, alkaline, 58 Å) instead of Al_2O_3 (alkaline, 200–300 mesh) was used as the additive. [e] **1a**/**2a**/**3a** = 1.0:1.8:1.2. [f] **1a**, **3a**, 4 Å M.S. and the additive was stirred for 2 h in CH_2Cl_2 before catalyst and **2a** were added.

Table 2: Substrate scope for the aza-Michael addition/ylide generation/intramolecular aldol addition pathway.[a]



Entry	$Ar^1/Ar^2/Ar^3$	R	**4**	Yield [%][b]	d.r.[c]
1	Ph/Ph/Ph	Me	**4a**	88	93:7
2	Ph/Ph/Ph	*i*Pr	**4b**	68	91:9
3	Ph/Ph/Ph	Bn	**4c**	46	90:10
4	*p*-BrC_6H_4/Ph/Ph	Me	**4d**	74	85:15
5	*m*-BrC_6H_4/Ph/Ph	Me	**4e**	68	84:16
6	*p*-FC_6H_4/Ph/Ph	Me	**4f**	60	86:14
7	*p*-MeC_6H_4/Ph/Ph	Me	**4g**	85	87:13
8	*p*-MeOPh/Ph/Ph	Me	**4h**	74	86:14
9	*p*-ClC_6H_4/Ph/Ph	Et	**4i**	72	88:12
10	Ph/*p*-BrC_6H_4/Ph	Me	**4j**	71	88:12
11	Ph/*m*-BrC_6H_4/Ph	Me	**4k**	64	90:10
12	Ph/*p*-MeC_6H_4/Ph	Me	**4l**	88	90:10
13	Ph/*p*-$MeOC_6H_4$/Ph	Me	**4m**	92	89:11
14	Ph/2-thienyl/Ph	Me	**4n**	40	88:12
15	Ph/Ph/*p*-ClC_6H_4	Me	**4o**	72	87:13
16	Ph/Ph/*p*-$NO_2C_6H_4$	Me	**4p**	93	85:15
17	Ph/Ph/*p*-$MeOC_6H_4$	Me	**4q**	89	87:13

[a] Unless otherwise noted, the reaction was carried out on a 0.30 mmol scale (**1**/**2**/**3** = 1.0:1.8:1.2). The mixture of **1** (0.30 mmol), **3** (0.36 mmol), 4 Å M.S. (300 mg), and Al_2O_3 (activated, alkaline, 58 Å) (0.30 mmol) in 1.5 mL of CH_2Cl_2 was stirred for 2 h at 40 °C before $[Rh_2(OAc)_4]$ was added, then **2** (0.54 mmol) in 1.5 mL of CH_2Cl_2 was added to the above mixture by syringe pump over 1 h. [b] Combined yield of isolated **4** and 3-*epi*-**4**. [c] The d.r. value of **4**/3-*epi*-**4** was determined by ^1H NMR spectroscopy of the crude reaction mixture.

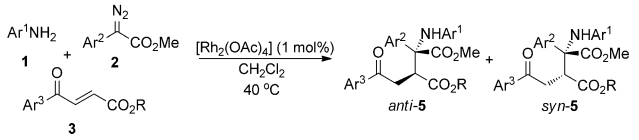
To facilitate the aza-Michael addition between **1a** and **3a** to form **6a**, different types of alkaline Al_2O_3 were tested as inexpensive and easily accessible additives to promote the reaction.[11] Initial screening revealed that reacting **1a** and **3a** for 1 hour in CH_2Cl_2 at 40 °C before the addition of $[Rh_2(OAc)_4]$ and **2a** was sufficient for achieving **4a** in good yield (78 %) and high diastereomeric ratio (93:7; Table 1, entries 2–4).[12] Since a certain amount of dimerization product of **2a** has been observed, the ratio of **1a**/**2a**/**3a** was adjusted to 1.0:1.8:1.2. This improved the yield of **4a** to 83 % (Table 1, entry 5). Increasing the reaction time for the aza-Michael addition between **1a** and **3a** from 1 to 2 hours provided an additionally improved yield (Table 1, entry 6). It is worth mentioning that the Al_2O_3 additive used in this one-pot, three-component reaction not only accelerated the formation of **6a**, but also improved the diastereoselectivity (Table 1 versus Scheme 2).

Under the optimized reaction conditions, a variety of substituted anilines, aryl diazoacetates, and 4-oxo-enoates were used for investigating the substrate generality of this aza-Michael addition/ylide generation/intramolecular aldol addition sequence. Ester groups on the 4-oxo-enoates were firstly investigated, and the highest yield as well as diastereoselectivity was obtained with a methyl group, whereas the use of either an isopropyl or benzyl group gave lower yields, thus indicating a relatively strong steric effect associated with the ester group (Table 2, entries 1–3). Anilines bearing different substituents were also investigated, and the results indicated that more-electron-rich aryl amines gave higher yields with similar diastereoselectivities (Table 2, entries 4–9). Diazo compounds bearing electron-rich aromatic rings also gave higher yields (Table 2, entries 12 and 13 versus entries 10 and 11). With methyl 2-diazo-2-(thien-2-yl)acetate as a substrate, the desired product **4n** was obtained in 40 % yield with a 88:12 diastereomeric ratio (Table 2, entry 14). Reactions with substituted 4-oxo-enoates revealed that substrates bearing more electron-deficient aromatic rings gave higher yields, however, with slightly reduced diastereoselectivities (Table 2, entries 15–17).

In contrast, inspired by the success in controlling the reaction pathway which exclusively led to the formation of **4a** through an adjustment in the addition sequence of reactants, we tried to tune the reaction to proceed by the ylide generation/Michael addition pathway (Scheme 1, path 2) through a similar protocol. As such, to avoid the unwanted formation of **6a**, **1a** was premixed with **2a** before this mixture was further added to the 4-oxo-enoate **3a** and 1 mol % $[Rh_2(OAc)_4]$. By using such an addition sequence, the formation of **6a** was not observed, however, the desired α-amino ester-derived product **5a** was afforded in only a 20 %

yield, along with the N–H insertion product between **1a** and **2a** as the major product.[13] To improve the yield of **5a**, optimization of the reaction conditions for this addition sequence was conducted. While the addition of 4 Å molecular sieves gave no improvement in terms of both the yield and diastereoselectivity, a thorough optimization of the reaction conditions, including the screening of solvents, temperatures, and adjustment of the ratio of **1a**/**2a**/**3a**, gave the following as the optimized reaction conditions: **1a**/**2a**/**3a** = 1.4:1.6:1.0 with CH_2Cl_2 as the solvent at 40 °C. The product **5a** was isolated in 87% yield with 90:10 diastereomeric ratio (Table 3, entry 1).[13]

Table 3: Substrate scope for the ylide generation/Michael addition pathway.[a]

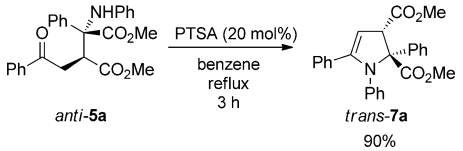


Entry	$Ar^1/Ar^2/Ar^3$	R	5	Yield [%][b]	d.r. (*anti*/*syn*)[c]
1	Ph/Ph/Ph	Me	**5a**	87	90:10
2	Ph/Ph/Ph	*i*Pr	**5b**	78	90:10
3	Ph/Ph/Ph	Bn	**5c**	67	89:11
4	*p*-BrC_6H_4/Ph/Ph	Me	**5d**	61	92:8
5	*m*-BrC_6H_4/Ph/Ph	Me	**5e**	70	88:12
6	*p*-FC_6H_4/Ph/Ph	Me	**5f**	75	88:12
7	*p*-MeC_6H_4/Ph/Ph	Me	**5g**	57	88:12
8	*p*-$NO_2C_6H_4$/Ph/Ph	Me	**5h**	53	92:8
9	*p*-ClC_6H_4/Ph/Ph	Et	**5i**	81	88:12
10	Ph/*p*-BrC_6H_4/Ph	Me	**5j**	86	87:13
11	Ph/*m*-BrC_6H_4/Ph	Me	**5k**	78	88:12
12	Ph/*p*-MeC_6H_4/Ph	Me	**5l**	88	86:14
13	Ph/*p*-$MeOC_6H_4$/Ph	Me	**5m**	74	83:17
14	Ph/2-thienyl/Ph	Me	**5n**	88	80:20
15	Ph/Ph/*p*-ClC_6H_4	Me	**5o**	73	88:12
16	Ph/Ph/*p*-$NO_2C_6H_4$	Me	**5p**	81	85:15
17	Ph/Ph/*p*-$MeOC_6H_4$	Me	**5q**	77	92:8

[a] Unless otherwise noted, the reaction was carried out on a 0.30 mmol scale (**1**/**2**/**3** = 1.4:1.6:1.0). A mixture of **2** (0.48 mmol) and **1** (0.42 mmol) in 1.5 mL of CH_2Cl_2 was added to a mixture of $[Rh_2(OAc)_4]$ (1 mol%) and **3** (0.30 mmol) in 1.5 mL of CH_2Cl_2 at 40 °C by syringe pump over 1 h. [b] Yield of isolated **5**. [c] Determined by HPLC.

With the optimized reaction conditions, the substrate scope for this ylide generation/Michael addition pathway was also investigated. With different ester groups on the 4-oxo-enoates, the yields were slightly reduced with more sterically hindered groups while the diastereoselectivities remained unaffected (Table 3, entries 1–3). When different anilines and aryl diazo compounds were investigated, the desired products were achieved in moderate to good yields with high diastereoselectivities (Table 3, entries 4–13). When methyl 2-diazo-2-(thien-2-yl)acetate was chosen as the substrate, the desired three-component product **5n** was obtained in 88% yield with an 80:20 diastereomeric ratio (Table 3, entry 14). The product yields were found to be roughly dependent on the electronic features of the substituents on the aryl ring of 4-oxo-enoates, with more-electron-deficient substrates giving higher yields with slightly lower diastereoselectivities (Table 3, entries 15–17).

The α-amino-ester-derived product obtained from the ylide generation/Michael addition pathway was readily cyclized under acidic conditions, thus providing the 2,3-dihydropyrrole *trans*-**7a** in nearly quantitative yield (Scheme 3).



Scheme 3. Synthesis of the 2,3-dihydropyrrole *trans*-**7a**. PTSA = *para*-toluenesulfonic acid.

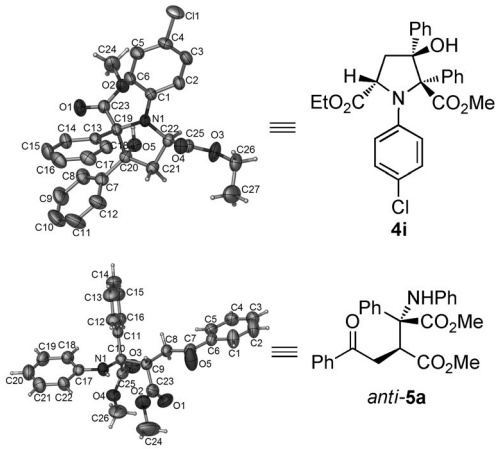
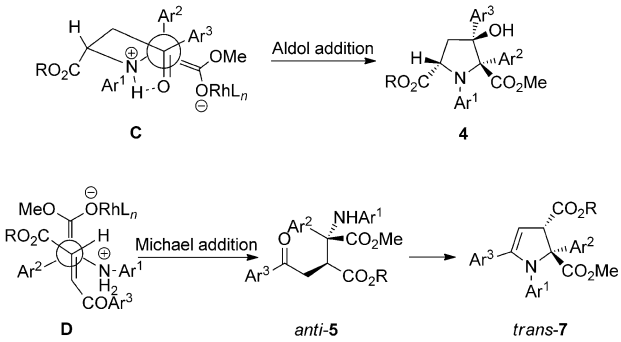


Figure 1. X-ray crystal structures of **4i** and *anti*-**5a**.[14]

The relative stereochemistry of the products was determined by single-crystal X-ray diffraction analysis (Figure 1). To explain the high diastereoselectivities achieved in each of the two reaction pathways, plausible preferential conformations for transition states of both reaction pathways were proposed (Scheme 4). In the aza-Michael addition/ylide generation/intramolecular aldol addition pathway, we proposed that an intramolecular hydrogen bond in intermediate



Scheme 4. Plausible preferential conformations for transition states.

C is the key aspect accounting for both the increased reactivity of the ketone carbonyl group as well as the good diastereoselectivity control. At the same time, the intramolecular hydrogen bonding could also slow down the undesired 1,2-proton shift. In contrast, in the ylide generation/Michael addition pathway, the intermediate **D** should have the preferential conformation, as shown in Scheme 4, and would be eventually transferred into the *anti*-product as the major product.

In summary, we have developed a three-component reaction of diazo compounds with anilines and 4-oxo-enoates by a switch in the reaction pathway. By controlling the addition sequence of the substrates, this three-component reaction can proceed through either an aza-Michael addition/ylide generation/intramolecular aldol addition pathway to generate pyrrolidines, or a ylide generation/Michael addition pathway to form linear α-amino ester derivatives. Divergent polyfunctional products from both reaction pathways are obtained in good yields with high diastereoselectivities. This pathway-switchable three-component reaction provides a unique platform for the divergent synthesis of either densely substituted nitrogen-containing linear molecules or heterocycles starting from the same reactants, and could be used in medicinal chemistry and pharmaceutical discovery for the rapid construction of compound libraries. Related research focusing on the asymmetric controls as well as the biological evaluations of those compounds is currently underway in our laboratory.

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[7] Reaction conditions: **2a** (0.24 mmol) in CH_2Cl_2 (1.0 mL) was added to a mixture of **1a** (0.22 mmol), **3a** (0.20 mmol), [$Rh_2(OAc)_4$] (1 mol%), and 4 Å M.S. (200 mg) in CH_2Cl_2 (1.0 mL) over a period of 1 h by syringe pump at 40 °C.

[8] Aza-Michael-type additions between aniline and 4-oxo-enoate catalyzed by N-heterocylic carbenes have been reported: Q. Kang, Y. G. Zhang, *Org. Biomol. Chem.* **2011**, *9*, 6715.

[9] Because of the complexity of this reaction system, the corresponding yields as well as diastereomeric ratios of each products were not determined.

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[12] For detailed optimization of the reaction conditions, see Table S1 in the Supporting Information.

[13] For detailed optimization of the reaction conditions, see Table S2 in the Supporting Information.

[14] CCDC 934227 (**4i**) and CCDC 934226 (*anti*-**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

