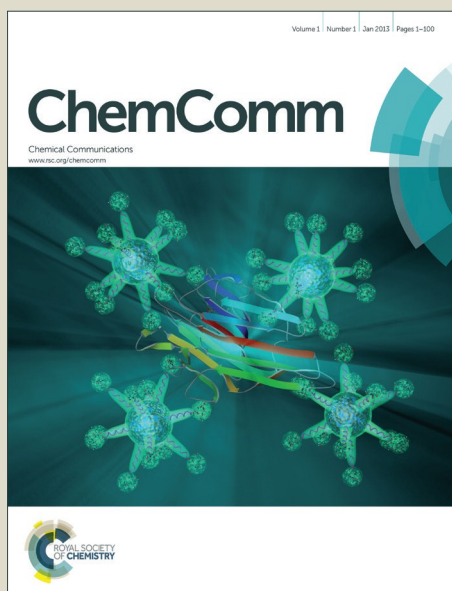


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Enantioselective Three-component Reaction of Diazoacetates with Indoles and Enals by Iridium/Iminium Co-catalysis

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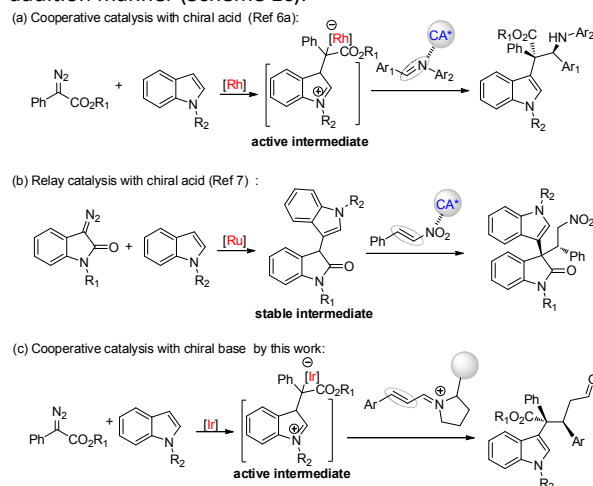
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The first example of chiral secondary amine and iridium(I) co-catalyzed enantioselective three-component reaction of aryldiazoacetates, indoles and enals was rationally designed and developed to afford 3-substituted indole derivatives in good yields and with moderate diastereoselectivity as well as excellent enantioselectivity. This reaction is proposed to proceed through the enantioselective trapping of iridium(I)-associated zwitterionic intermediates via selective 1,4-addition to the chiral amine activated enals.

Asymmetric multi-component reaction (AMCR) is a powerful tool for the efficient and stereoselective construction of structurally complex chiral molecules in modern organic synthesis.¹ Although several excellent enantioselective MCRs have been well developed,² rational design of highly enantioselective MCRs remains a long lasting challenge³ and is limitedly established mainly owing to the challenge to establish a compatible catalytic system to address both the chemoselective control and enantioselective control of the desired process.

By raising the HOMO of nucleophiles and lowering the LUMO of electrophiles simultaneously with a combination of different catalysts to achieve matched reactivity, cooperative catalysis is well established as an efficient strategy for promoting unprecedented MCRs.⁴ Since 2008, our group has developed a set of enantioselective MCRs by trapping of active onium ylides⁵ or zwitterions⁶ with appropriately activated electrophiles for the rapid construction of polyfunctional chiral molecules. For instance, the active zwitterions *in situ* generated from aryldiazoacetates and indoles were trapped by chiral phosphoric acid activated imines to provide an

expedient access to polyfunctional indoles (Scheme 1a). However, the co-catalytic system of transition metals and chiral acids (CA*) often present insufficient activation of simple Michael acceptors to trap the active onium ylides or zwitterion intermediates, to give the desired 1,4-addition products. This challenge mainly arises from the mismatched reactivity of the active ylides/zwitterions and the activated trapping reagents for the desired reaction pathway. For example, only 1,2-addition products were observed in Rh(II) and Lewis acid co-catalyzed three-component reaction of phenyldiazoacetate, benzyl alcohol and cinnamaldehyde.^{5a} Recently, Gong et al. reported a three-component sequence of indoles, 3-diazoindole and nitroalkenes by a stepwise tandem ruthenium-catalyzed C-H insertion and squaramides-catalyzed 1,4-addition (Scheme 1b).⁷ Herein, we report an iridium complex and chiral secondary amine co-catalytic system enabling the activation of enals to promote an enantioselective MCR with diazoacetates and indoles in a 1,4-addition manner (Scheme 1c).



Scheme 1 Catalysis strategies for the development of MCRs.

Known as a covalent-bond-forming activation mode, iminium catalysis with primary or secondary amines is well established for the activation of α , β -unsaturated carbonyls.⁸ In

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[‡] Mingfeng Li and Xin Guo equally contributed to this work.

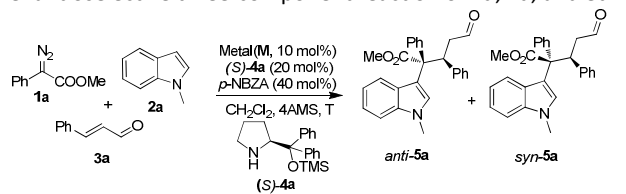
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order to sufficiently activate enals, chiral secondary amines such as diarylprolinol silyl ethers, were rationally considered to be used as co-catalysts in the ylide-trapping process. Although cooperative catalysis strategy of enamines and transition metals has been well demonstrated since 2006,⁹ cooperative catalysis involving iminium and transition metals is more recently developed and rather rare examples were reported since Córdova and his co-worker established a Cu(II) and chiral secondary amine co-catalyzed conjugate silyl addition of enals.¹⁰ The main challenge lies in the possible coordination of Lewis acidic metal and basic amines, which will lead to a self-quenching of both the catalysts. Additional great challenge in current trapping process is how to modulate the matched rate to generate the active reaction species. The diazo-decomposition process catalyzed by commonly used rhodium(II) complexes to generate the zwitterion intermediates is known as a rapid process. Compared to the non-covalent activation modes such as Lewis acid or Brønsted acid catalysis, the formation of iminium salts and hydrolysis of the enamine adduct involving multiple covalent bond-forming and bond-breaking events are slower processes even promoted by acidic additives.^{8,11} In order to achieve a matched generation rate of the active intermediates with iminium catalysis, a transition metal catalyst with much less catalytic efficiency for the diazo decomposition would be desired.

Iridium complexes have been well established as efficient catalysts for various transformations, and the combination of iridium complexes and enamine catalysis has been developed by the Carreira group for asymmetric α -allylation of aldehydes.¹² Meanwhile, several examples of employing iridium complexes to catalyze the decomposition of diazo compounds generating iridium-associated carbenes were reported.¹³ Thus, we envisioned that the combination of iridium complexes and chiral secondary amines may present a compatible catalytic activity to promote the trapping of active zwitterions generated in situ from diazo compounds and indoles with enals. To the best of our knowledge, no iridium and iminium co-catalyzed asymmetric reactions have been previously established.

Table 1 Reaction condition optimization for the enantioselective three-component reaction of **1a**, **2a**, and **3a** ^[a]



entry	M	T(°C)	t (hr)	yield (%) ^[b]	dr(<i>anti</i> : <i>syn</i>) ^[c]	ee(% <i>anti</i> / <i>syn</i>) ^[d]
1	[Ir(COD)Cl] ₂	r.t.	20	53	64:36	86/97
2	Rh ₂ (OAc) ₄	r.t.	2	42	50:50	76/95
3	[PdCl(η^3 -C ₃ H ₅)] ₂	r.t.	20	29	67:33	86/97
4	Cu(hfacac) ₂	r.t.	48	15	62:38	95/95

5	[Rh(COD)Cl] ₂	r.t.	2	0	--	--
6	Ir(COD) ₂ BF ₄	r.t.	48	20	61:39	86/97
7	[Ir(COE) ₂ Cl] ₂	r.t.	20	20	71:29	91/99
8	Ir(COD)(hfacac)	r.t.	20	47	66:34	84/97
9 ^[e]	[Ir(COD)Cl] ₂	r.t.	20	56	67:33	95/97
10 ^[e,f]	[Ir(COD)Cl] ₂	r.t.	20	45	66:34	94/96
11 ^[e]	[Ir(COD)Cl] ₂	40	15	40	57:43	91/93
12 ^[e]	[Ir(COD)Cl] ₂	0	24	71	76:24	97/97
13 ^[e]	[Ir(COD)Cl] ₂	-10	32	66	71:29	87/94

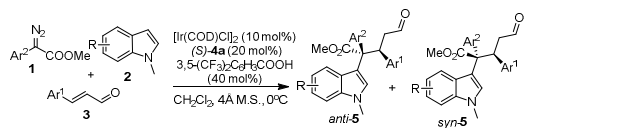
^[a] General reaction conditions: M:(*S*)-**4a**:*p*-NBZA:**1a**:**2a**:**3a**=0.1:0.2:0.4:2:2:1. ^[b] Isolated yield of *anti*- and *syn*-**5a**. ^[c] Determined by ¹H NMR analysis of the crude mixture. ^[d] Determined by chiral HPLC analysis. ^[e] Acid=3,5-(CF₃)₂C₆H₃COOH. ^[f] The amount of 3,5-(CF₃)₂C₆H₃COOH is 20 mol%.

The initial exploration was carried out by reacting methyl phenyldiazoacetate **1a**, indole **2a** and cinnamyl aldehyde **3a** in CH₂Cl₂ with [Ir(COD)Cl]₂ (10 mol%) and (*S*)-2-(diphenyl((trimethylsilyl)oxy)-methyl)pyrrolidine **4a** (20 mol%) as a co-catalyst and *p*-nitrobenzoic acid (*p*-NBZA, 40 mol%) as an additive. Encouragingly, the reaction was finished in 20 hrs and the desired 1,4-addition product **5a** was obtained in 53% yield and with moderate dr (*anti*:*syn* = 64:36) and high ee (86% ee for *anti*-**5a**, 97% ee for *syn*-**5a**) (Table 1, entry 1). The main side product was the C-H insertion product **9** derived from reaction of **1a** and **2a**, and no three-component 1,2-addition product was observed. For comparison, other commonly used transition metal catalysts for the decomposition of diazo compounds, such as Rh₂(OAc)₄, [PdCl(η^3 -C₃H₅)]₂¹⁴ and Cu(hfacac)₂¹⁵ were also investigated. As anticipated, Rh₂(OAc)₄ catalyzed a much faster reaction to give product **5a** but in a lower yield and with decreased stereoselectivity (Table 1, entry 2). The lower yield of the three-component product may be attributed to a faster zwitterion-generation rate than that promoted by Ir(I) catalyst leading to more C-H insertion product.¹⁶ Both [PdCl(η^3 -C₃H₅)]₂ and Cu(hfacac)₂ were much less effective to promote this reaction in a lower yield of 29% and 15%, respectively (Table 1, entries 3-4). [Rh(COD)Cl]₂ gave no desired product but produced only the C-H insertion product (Table 1, entry 5). Varying the counter anions or ligands in iridium complexes afforded lower yields but remained a similar stereoselectivity (Table 1, entries 6-8). Other amine co-catalysts with different diarylprolinol silyl ethers showed a negligible improvement to the reaction (see Supporting Information, Table S1). The effect of a number of acid additives on the reaction was also investigated (see Supporting Information, Table S2). Strong acids such as trifluoro acetic acid (TFA) and 4-methyl benzenesulfonic acid (TsOH) gave only the C-H insertion by-product (see Supporting

Information, Table S2), which is probably due to that these strong acids served as bifunctional proton-donor-acceptor catalyst to accelerate the 1,2-proton shift process.¹⁶ Among the substituted benzoic acids, 3,5-(CF₃)₂C₆H₃COOH was optimal and afforded the product in 56% yield and with 67:33 dr and 95% ee for *anti*-**5a**, 97% ee for *syn*-**5a** at room temperature (Table 1, entry 9). Lower yield of **5a** was obtained when decreasing the amount of the acid additive from 40 mol% to 20 mol% (Table 1, entry 10), indicating that the ratio of the amine and the acid additive is important. Screening of other solvents gave no obvious improvement in yield and stereoselectivity (see Supporting Information, Table S3). The reaction temperature was found to have a profound effect on the reaction (Table 1, entries 11-13), and the optimal reaction temperature was identified as 0 °C to give **5a** in 71% yield and with an improved dr (*anti*:*syn* = 76:24) and excellent ee value (97% ee for both *anti*-**5a** and *syn*-**5a**) (Table 1, entry 13).

With the optimal reaction conditions in hand, substrate scope for this iridium and chiral amine co-catalyzed three-component reaction was examined, and the results are summarized in Table 2. In general, the reaction tolerates various substitutions on the aromatic or heteroaryl rings of enals **3** (entries 1-5), diazo compounds **1** (entries 6-12) and indoles **2** (entries 13-16). In most cases, moderate to good yields (up to 80%) were obtained with a moderate dr ratio (*anti*:*syn* up to 78:22) and an excellent enantioselectivity (up to 98% ee). However, the reaction process seems to be sensitive to steric effect, as *o*-Br substituted phenyl diazoacetate led to only the C-H insertion side product and a total recovery of cinnamaldehyde (Table 2, entry 12), while *p*-Br substituted one gave desired product in 53% yield (Table 2, entry 8). Absolute configurations of the major isomer *anti*-**5n** and the minor isomer *syn*-**5b** were determined by single crystal X-ray crystallography as (2*S*, 3*S*) and (2*S*, 3*R*), respectively (see ESI). That of other products was then assigned by analogy.

Table 2 Substrate scope of Iridium/Lewis base co-catalyzed three-component reaction [a]

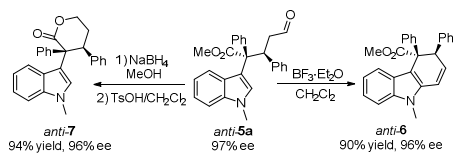


entry	Ar ¹	Ar ²	R	5	yield (%) ^[b]	dr(<i>anti</i> / <i>syn</i>) ^[c]	ee(%) ^[d]
1	Ph	Ph	H	5a	71	76:24	97/97
2	<i>p</i> -BrC ₆ H ₄	Ph	H	5b	60	77:23	96/95
3	<i>p</i> -MeC ₆ H ₄	Ph	H	5c	58	73:27	96/82
4	<i>m</i> -MeC ₆ H ₄	Ph	H	5d	47	78:22	98/98
5	2-furanyl	Ph	H	5e	60	62:38	90/94
6	Ph	<i>p</i> -FC ₆ H ₄	H	5f	70	68:32	97/97
7	Ph	<i>p</i> -ClC ₆ H ₄	H	5g	62	59:41	94/99
8	Ph	<i>p</i> -BrC ₆ H ₄	H	5h	56	52:48	94/97

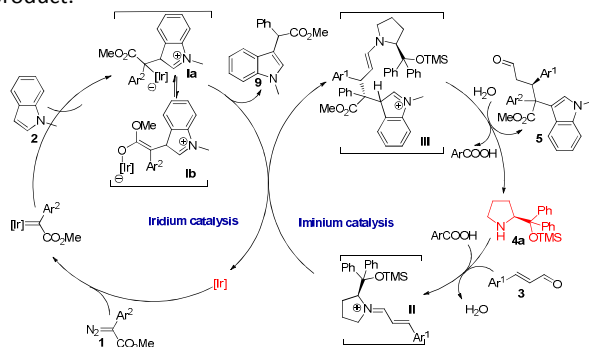
9	Ph	<i>p</i> -MeC ₆ H ₄	H	5i	71	69:31	96/98
10	Ph	<i>p</i> -MeOC ₆ H ₄	H	5j	63	71:29	94/99
11	Ph	<i>m</i> -MeOC ₆ H ₄	H	5k	75	59:41	98/99
12	Ph	<i>o</i> -BrC ₆ H ₄	H	--	0	--	--
13	Ph	Ph	5-F	5l	80	69:31	97/98
14	Ph	Ph	5-Cl	5m	75	66:34	98/99
15	Ph	Ph	5-Br	5n	49	60:40	95/73
16	Ph	Ph	7-Br	5o	34	66:34	98/94

[a] General reaction conditions: [Ir(COD)Cl]₂:(S)-**4a**:3,5-(CF₃)₂C₆H₃COOH:**1a**:**2a**:**3a**=0.1:0.2:0.4:2:2:1. [b], [c], [d]: Reaction conditions as performed in Table 1.

The synthetic applications of the three-component products were illustrated by an intramolecular ring closure to yield fused *N*-heterocycle **6** with BF₃·Et₂O in CH₂Cl₂, or by a simple reduction of the aldehyde group to hydroxyl group with NaBH₄ followed by an intramolecular transesterification to afford the corresponding 3-substituted indole **7** (Scheme 2). Both **6**¹⁷ and **7**¹⁸ serve as a pivotal structural moiety in pharmaceutical research.



Scheme 2 Synthetic application of the three-component product.



Scheme 3 Proposed reaction mechanism of the Iridium/iminium co-catalyzed three-component reaction.

To get insight into the reaction mechanism, control experiments were conducted. A reaction of the C-H insertion product and cinnamaldehyde under the standard conditions gave no 1,4-addition product, excluding a stepwise tandem process of the three-component reaction. In the absence of (S)-**4a** or *p*-NBZA co-catalysts, the reaction gave only the C-H insertion side product together with total recovery of cinnamaldehyde. LC-MS spectra of the reaction mixture solution also confirmed the generation of iminium cation from **3** and **4a** (see Supporting Information, Figure S1). On the basis

of the abovementioned investigations, a possible mechanism was proposed and outlined in Scheme 3. The zwitterionic intermediate **1a** or enolate **1b** was formed *in situ* from the iridium catalyzed diazo decomposition of **1** and **2**. For the iminium catalysis, the additive acid accelerates the formation of an iminium ion **II**, which effectively trap the zwitterionic intermediate **I** to afford an enamine **III**. Acid promoted hydrolysis of **III** yields the three-component coupling product **5** and regenerates chiral amine **4a**.

In conclusion, an iridium complex/chiral amine co-catalyzed three-component reaction of diazoacetates, indoles and enals was successfully developed to give functionalized indole derivatives in good yields and with a moderate diastereoselectivity and excellent enantioselectivity (up to 98% ee). The novel iridium and iminium co-catalysis promoted enals to successfully trap the active zwitterionic intermediate in a regioselective 1,4-addition fashion. The matched reactivity of intermediates **I** and **II** and the comparable catalytic rate of the two catalytic cycles are believed to be critical for the success of the current trapping process.

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