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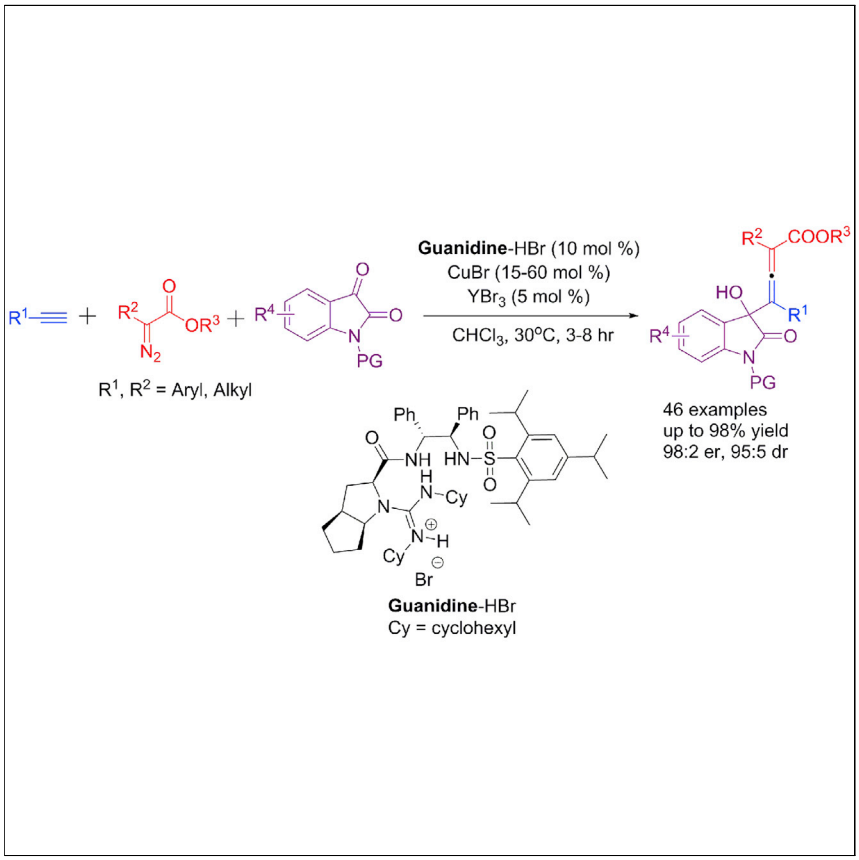
Asymmetric Three-Component Reaction for the Synthesis of Tetrasubstituted Allenoates via Allenoate-Copper Intermediates



We developed an efficient and direct route for the synthesis of tetrasubstituted allenes via asymmetric multicomponent reaction (AMCR) by utilizing a variety of α-diazoesters, terminal alkynes, and isatins. This method enables Cu(I)-involved AMCRs of α-diazo compounds and also gives solid experimental evidence for the formation of allenoate-Cu(I) intermediates in C–H insertion of α-diazoesters to terminal alkynes. Combined-acid systems of guanidinylated metal complexes lead to higher reactivity and equally effective asymmetric environment.

Yu Tang, Jian Xu, Jian Yang, Lili Lin, Xiaoming Feng, Xiaohua Liu

liuxh@scu.edu.cn

HIGHLIGHTS

Asymmetric three-component reaction of α-diazoesters, terminal alkynes, and isatins

Synthesis of tetrasubstituted allenes bearing axial and central chirality

Solid evidence of allenoate-copper intermediates in C–H insertion

Mechanism study of combined-acid systems

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Asymmetric Three-Component Reaction for the Synthesis of Tetrasubstituted Allenoates via Allenoate-Copper Intermediates

Yu Tang,[1] Jian Xu,[1] Jian Yang,[1] Lili Lin,[1] Xiaoming Feng,[1] and Xiaohua Liu[1,2,*]

SUMMARY

A catalytic asymmetric three-component reaction of α-diazoesters with terminal alkynes and isatins was achieved. This one-pot synthesis gave rise to axially chiral tetrasubstituted allenoates bearing a stereogenic center. The chiral guanidinium salt/CuBr/YBr_3 catalytic system proved efficient and highly diastereo- and enantioselective for a wide range of alkynes, aromatic α-diazoesters, and isatins under mild reaction conditions. This approach enables a Cu(I)-involved asymmetric multicomponent reaction (AMCR) of α-diazo compounds and gives solid experimental evidence for the formation of allenoate-Cu(I) intermediates in C–H insertion of α-diazoesters to terminal alkynes. We also found that additional acids improved the catalyst efficiency of guanidinium salt/CuCl in the direct enantioselective C–H insertion of α-aryl diazoesters. Mechanism studies suggest that the combined-acid systems (Lewis acid combined with assisted Lewis acid or Brønsted acid combined with assisted Lewis acid) bring out higher reactivity by associative interaction and allow for an equally effective asymmetric environment.

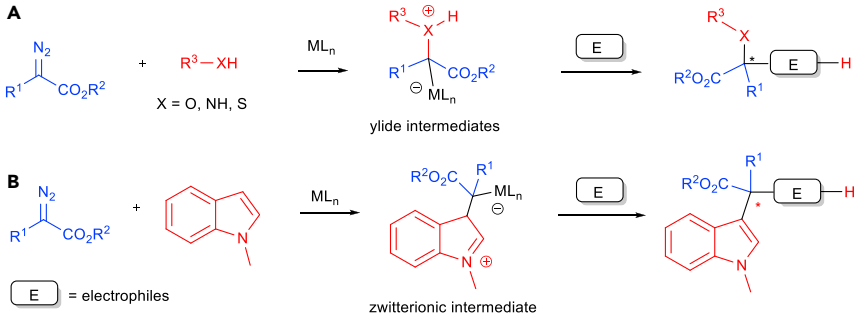
INTRODUCTION

The asymmetric multicomponent reaction (AMCR) has emerged as a powerful tool to synthesize structural complicate chiral compounds with greater efficiency and atom-economy.[1–9] One way to achieve AMCRs is to trap an active intermediate generated from two reactants with the third component.[10–18] Ylide species formed from hetero atom-H insertion (such as alcohols,[12] amines,[13] and mercaptides[14]) with α-diazo compounds have been utilized to react with electrophiles to construct polyfunctional molecules (Scheme 1A). Zwitterionic intermediates generated from the Csp^2-H insertion reaction of α-diazocarbonyl compounds to indoles[16] (Scheme 1B), or *N*,*N*-disubstituted anilines[17] could also participate in AMCRs. These processes have been well documented by several research groups independently,[18] and the use of dirhodium complexes to generate ylide or zwitterionic intermediates proves to be the general strategy given the fact that rhodium-carbene enables delayed proton transfer.[11–18] Only a few examples show that copper(I) salts allow the MCRs of diazo compounds, but no asymmetric catalytic version has been realized.[15] Moreover, AMCRs via trapping of intermediates from C–H insertion are less developed than those from O–H and N–H insertions.[11–18] For example, catalytic asymmetric C*sp*-H insertions of diazo compounds into terminal alkynes to generate axially chiral tri- and disubstituted allenes were realized recently.[19–21] Nevertheless, the reaction process remains disputed and no experiment has yet been performed to trap the possible intermediates.[19–25]

Chiral allenes represent a type of three-carbon axially chiral skeleton and have attracted increasing attention.[26–45] Limited examples have been reported in

The Bigger Picture

Chirality is a universal phenomenon found in nature. Different from the usual central chirality, allenes are a class of compounds bearing three-carbon axially chiral skeletons and have attracted increasing attention for their usefulness as synthetic intermediates. This unique structural feature can provide allenes with specific biological activity and has been found in many drug molecules and natural products; thus, there is increasing demand for new routes toward these pharmaceutically relevant compounds. Nevertheless, the catalytic asymmetric synthesis of axially chiral allenes, especially for tetrasubstituted ones, is still in its infancy. Here, we report the synthesis of tetrasubstituted allenoates via an asymmetric three-component reaction of α-diazoesters with terminal alkynes and isatins. This gives access to the desired central and axial chirality bearing carbinol allenoate by trapping the corresponding allenoate-copper intermediate with isatin.



Scheme 1. AMCRs via Trapping of Intermediates from X–H or C–H Insertion of Diazocarbonyl Compounds

Trapping of ylide intermediates (A) and zwitterionic intermediates (B).

asymmetric catalytic synthesis of tetrasubstituted allenes[46–49] in comparison with the achievement of di- and trisubstituted allenes.[34–45] Asymmetric nucleophilic addition with allenic ester or its isomeric compound is useful for the construction of tetrasubstituted allenic derivatives bearing both axial and central chirality.[46–49] Alleno-Mannich-type reactions via phase-transfer catalysis[46] or peptide catalysis[47] (Scheme 2, equation 1), as well as alleno-aldol-type reaction by chiral *N*,*N*′-dioxide/Au(III) catalysis[48] (Scheme 2, equation 2) gave α- and γ-regioselective products, respectively. Alternatively, an enantioselective alkynylogous Mukaiyama aldol reaction worked well for this purpose (Scheme 2, equation 3).[49] However, for these pioneering achievements, racemic trisubstituted allenoates or ketene acetals should be prepared beforehand. The substituents of allenoate products are general aliphatic ones, and the relative stability between alkynoate-allenoate isomeric pairs is affected by the linking groups,[46–48] thus affecting the reaction activity and enantioselectivity.

Our group initially developed chiral guanidinium salt and Cu(I) salt-promoted asymmetric C–H insertion of α-diazoesters to construct tri-substituted allenes.[19] We proposed that the reaction might enantioselectively generate allenoate-Cu(I) intermediate after proton transfer to give the allenoate product. If this intermediate could be trapped by an electrophile before H-shift, a direct synthesis of tetrasubstituted allenic derivatives could be available via a new AMCR (Scheme 2C). Nevertheless, such a process is challenging because of possibly competitive pathways, including alkynylation of the electrophile,[50] H-transfer to yield alkyne or trisubstituted allenoate,[19–21] and trapping of alkynoate-copper intermediate (Scheme 2C) among others. The control of selectivity is also attractive as both stereogenic center and axial chirality should be in control simultaneously. The challenge lies in avoiding racemization from central chirality to axial chirality via 1,3-copper shift, and discovering more-organized chiral structures that allow an enantioselective nucleophilic addition to isatin.

Herein, we discover that in the presence of a catalytic amount of chiral guanidinium salt, CuBr, and YBr_3 catalysts, AMCRs among aromatic α-diazoesters, aryl- or alkyl-substituted terminal alkynes, and isatin derivatives perform well under mild reaction conditions. The desired carbinol allenoates are afforded in good to excellent yields, diastereoselectivities, and enantioselectivities for a wide range of substrates. Aryl groups were readily introduced into the substituents of alkynoates, which is a useful complementation to previous strategies.[46–49] Furthermore, this AMCR provides solid experimental evidence for the formation of allenoate-Cu(I) intermediate via 1,3-copper shift from alkynylcopper intermediate in the C–H insertion of terminal alkynes with α-diazoesters. With regard to the chiral catalyst system, this reveals

[1]Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P.R. China

[2]Lead Contact

*Correspondence: liuxh@scu.edu.cn

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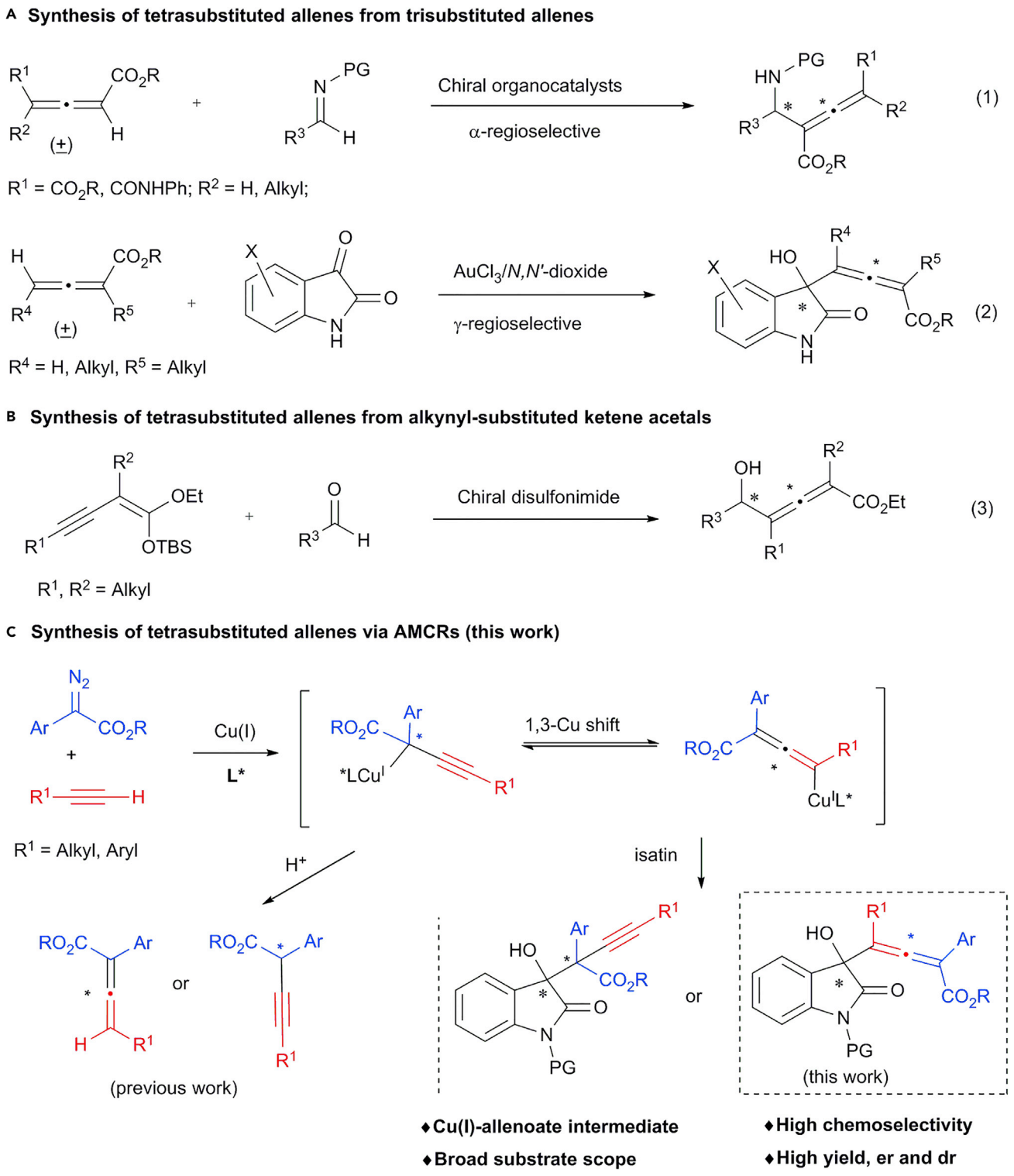

Scheme 2. Asymmetric Catalytic Synthesis of Tetrasubstituted Allenoates

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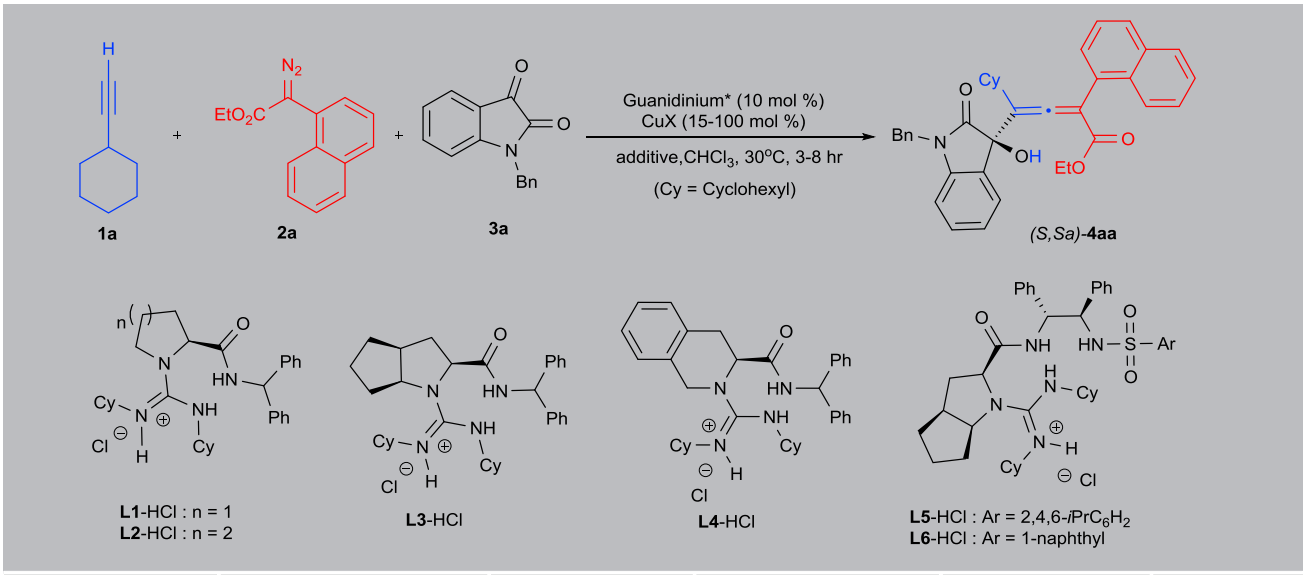
Table 1. Optimization of the Reaction Conditions



Entry[a]	Guanidinium	CuX	Yield (%)[b]	dr[c]	er[d]
1	L1-HCl	CuCl	41	63:37	85:15/63:37
2	L2-HCl	CuCl	19	45:55	67:33/56:44
3	L3-HCl	CuCl	27	61:39	88:12/70:30
4	L4-HCl	CuCl	7	49:51	68:32/58:42
5	L5-HCl	CuCl	24	78:22	97:3/71:29
6	L6-HCl	CuCl	14	84:16	96:4/87:13
7	L5-HI	CuI	31	80:20	94:6/76:24
8	L5-HBr	CuBr	76	80:20	98:2/75:25
9[e]	L5-HBr	CuBr	42	80:20	98:2/75:25
10[e,f]	L5-HBr	CuBr	71	80:20	98:2/74:26
11[e,f,g]	L5-HBr	CuBr	94	80:20	98:2/74:26

[a]Unless otherwise noted, all reactions were carried out with CuX (100 mol %), guanidinium salt (10 mol %), **1a** (0.10 mmol), **2a** (1.2 equiv), and **3a** (1.0 equiv) in $CHCl_3$ (0.6 mL) at 30°C for 3 hr (see Tables S1–S6 for details). The absolute configuration of **4aa** was determined by comparison with the CD spectra of **4hc** (see also Figures S5, S6, and S8).
[b]Isolated yield.
[c]Determined by ^1H NMR.
[d]Determined by high-performance liquid chromatography (HPLC).
[e]CuBr (15 mol %), 8 hr.
[f]YBr_3 (5 mol %).
[g]**2a** (1.5 equiv) in $CHCl_3$ (0.2 mL).

that Brønsted acid as hydrogen halide (BLA) or Lewis acid as YBr_3 (LLA) increases the reactivity of the chiral guanidine-Cu(I) complex. The BLA or LLA combined-acid system[51–53]addresses the issue that an excessive amount of copper salt was used in previous C–H insertion of α-diazoesters to terminal alkynes.[19]

RESULTS AND DISCUSSION

We initially examined conditions on the basis of those we reported for the C–H insertion of α-diazoester with terminal alkyne,[19] employing isatin as the electrophile to trap the possible intermediates, because isatin is an active electrophile and oxindole derivatives present a type of unique biologically active structures.[54] Table 1 outlines optimization studies for a model AMCR among alkyne **1a**, α-naphthyl substituted

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α-diazoester **2a**, and *N*-Bn protected isatin **3a** (see Tables S1–S9 for details). Chiral guanidinium salt (10 mol %) and 1.0 equiv of CuCl were used as the catalyst, and the desired three-component reaction product **4aa** via trapping of allenoate-Cu(I) intermediate could be detected, albeit the reactivity and selectivity was poor. A screen of a series of hydrochloride salts of guanidine-amides **L1–L4** revealed that *L*-proline- and *L*-ramipril-derived guanidine **L1** and **L3** could provide somewhat better yield and selectivities (Table 1, entries 1–4). Considering the participation of isatin **3a**, which will raise issues including activity of nucleophilic addition and formation of a stereogenic center, we introduced guanidine **L5** and **L6** bearing sulfonamide substituent (Table 1, entries 5 and 6),[50,55,56] allowing us to activate and fix isatin with an intermolecular H-bonding (see Figure S4 for details). To our delight, experimentally significant diastereo- and enantioselectivity with a maximum enantiomeric ratio (er) of 97:3 and 24% yield was obtained with 2,4,6-triisopropylbenzenesulfonamide-substituted guanidinium salt **L5**-HCl (Table 1, entry 5). We changed the salt of guanidine and copper into **L5**-HBr and CuBr, resulting in a yield of 76%, 80:20 diastereomeric ratio (dr), and 98:2 er for the major diastereomer (Table 1, entries 5, 7, and 8; see Table S2 for details). An attempt to decrease the amount of CuBr to 15 mol % led to a dropped yield of 42% (Table 1, entry 9). We initially wondered whether additional Lewis acid could suppress the interaction between CuBr and the carbonyl groups of isatin and α-diazoester, thus reducing the amount of CuBr. Indeed, the addition of 5 mol % of YBr_3 resulted in formation of the desired product **4aa** in 71% yield with maintained diastereo- and enantioselectivity in the presence of 10 mol % **L5**-HBr and 15 mol % CuBr (Table 1, entry 10). Increasing the amount of α-diazoester to 1.5 equiv and reducing the amount of solvent $CHCl_3$ provided a higher yield of 94% (Table 1, entry 11). Under these optimized conditions, AMCR product **4aa** was obtained in 94% yield, 98:2 er, and 80:20 dr. Trace amount of C–H insertion product[19] was detected in this route, and no alkynylation[50] or propargylation of isatin were observed (Scheme 2).

The applicability of this process to a broad range of aromatic α-diazoesters with cyclohexyl acetylene **1a** and isatin **3a** is shown in Table 2 (see Table S11, Schemes S11–S31, and Figures S6–S41 for details). For phenyl-substituted α-diazoesters, steric hindered *tert*-butyl ester showed higher reactivity and selectivity than ethyl ester (Table 2, entry 1 versus 2). The aryl moiety tolerated significant electronic perturbation: both electron-donating and -withdrawing substituents yielded the corresponding AMCR products in good yields and good diastereo- and enantioselectivities (Table 2, 84%–98% yield, 78:22 to 90:10 dr, and 94:6 to 98:2 er; entries 2–10). *Ortho*-halo-substituted *tert*-butyl α-diazo-phenylacetates gave better diastereoselectivities and yields than the others. The piperonyl-substituted α-diazoester **2k** had a deleterious effect on the reactivity, and 71% yield with 96:4 er and 83:17 dr was obtained (Table 2, entry 11) with a higher amount of CuBr. Furthermore, 1- or 2-naphthyl- or 2-thienyl-substituted α-diazoesters were tolerated such that the reaction proceeded smoothly in 88%–96% yield with comparably excellent enantioselectivity and diastereoselectivity (Table 2, entries 12–14). It is noteworthy that when ethyl 2-diazopropanoate **2s** was used in the AMCR with cyclohexyl acetylene **1a** and isatin **3a**, racemic carbinol pent-3-ynoate product **6sa** via trapping of alkynoate-copper intermediate was detected rather than carbinol allenoate product (Figure 1, equation 1; see Scheme S3 for details). Interestingly, the reaction among ethyl 2-diazopropanoate **2s**, ethynylbenzene **1g**, and isatin **3a** enable the formation of carbinol allenoate **4sg** with good yield and enantioselectivity, albeit the diastereoselection was poor (Figure 1, equation 2; see Scheme S3 for details). This indicates the formation of alkyl-substituted alknynoate-copper species, which might be more stable than the corresponding allenoate-copper species.

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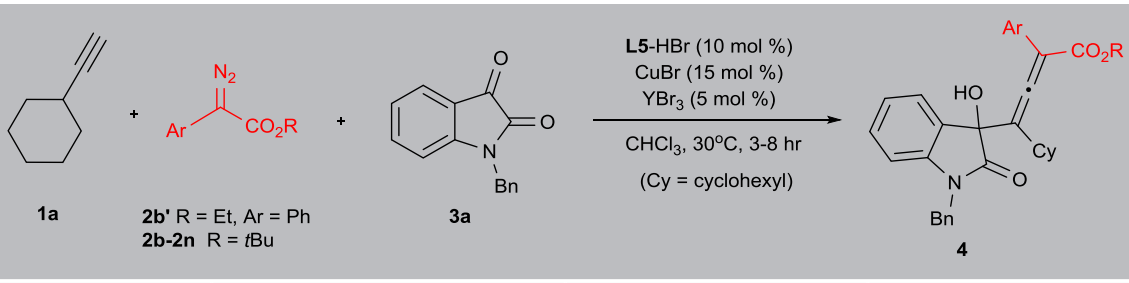
Table 2. Substrate Scope for α-Diazoesters



1a

2b' R = Et, Ar = Ph
2b-2n R = *t*Bu

3a

4

Entry[a]	2: Ar	Yield (%)	er	dr
1[b,d]	2b′: C_6H_5	27 (4b′a)	95:5	80:20
2[c,d]	2b: C_6H_5	90 (4ba)	97:3	80:20
3	2c: 2-MeC_6H_4	90 (4ca)	96:4	78:22
4[c,e]	2d: 3-MeC_6H_4	81 (4da)	96:4	83:17
5	2e: 4-MeC_6H_4	91 (4ea)	95:5	82:18
6	2f: 2-FC_6H_4	92 (4fa)	97:3	90:10
7	2g: 4-FC_6H_4	83 (4ga)	97:3	83:17
8	2h: 2-ClC_6H_4	98 (4ha)	98:2	90:10
9	2i: 2-BrC_6H_4	91 (4ia)	97:3	88:12
10	2j: 4-*t*BuC_6H_4	84 (4ja)	94:6	79:21
11[c,e]	2k: piperonyl	71 (4ka)	96:4	83:17
12	2l: 1-naphthyl	96 (4la)	96:4	80:20
13[c,d]	2m: 2-naphthyl	89 (4ma)	96:4	82:18
14	2n: 2-thienyl	88 (4na)	95:5	81:19

[a]Unless otherwise noted, the reactions were carried out on 0.1 mmol scale under the reaction condition of entry 11 in Table 1 for 3 hr.
[b]CuBr (60 mol %).
[c]CuBr (30 mol %).
[d]Reacting for 8 hr.
[e]Reacting for 5 hr.

The scope of this reaction with respect to isatin component is summarized in Table 3 (see Table S12, Schemes S32–S44, and Figures S42–S67 for details). Variation of isatins was studied with 2-chlorophenyl α-diazoester **2h** and alkyne **1a** as the substrates. Generally, isatins **3** bearing both electron-donating and -withdrawing groups provided the corresponding products **4hb** to **4hk** in excellent yields (88%–97%) and enantioselectivities (98:2 to 91:9 er; Table 3, entries 1–11). Excellent diastereoselectivity (95:5 dr) was obtained when 4-fluoro-, 4-chloro-, and 4-bromo-substituted isatins were inducted into the reaction (Table 3, entries 1–4). Changing the *N*-protecting group of isatin from Bn to other electron-donating groups (Me, PMB, and $BnCH_2$) had no significant influence on the results, but NH-free and *N*-Ts protected isatins were inert in the reactions (Table 3, entries 12–15). It is interesting to note that a gram-scale enantioselective synthesis of **4hc** could also be accommodated under the standard reaction condition (Table 3, entry 3; see Scheme S9 for details). The absolute configuration of the corresponding thiophene-2-carboxylate derivative **7hc** was established to be (*S*, S_a) by X-ray diffraction analysis (Figure S5 and Scheme S74)[57]; thus the major enantiomer of the product **4hc** was assigned to be (*S*, S_a). According to a comparison with the CD spectra of **4hc**, the absolute configurations of **4hb** and **4hd** were also determined as (*S*, S_a) (see Figures S153–S156 for details). In addition, terminal alkyne **1t** decorated with an aldehyde group could perform the C–H insertion and nucleophilic addition reaction, yielding

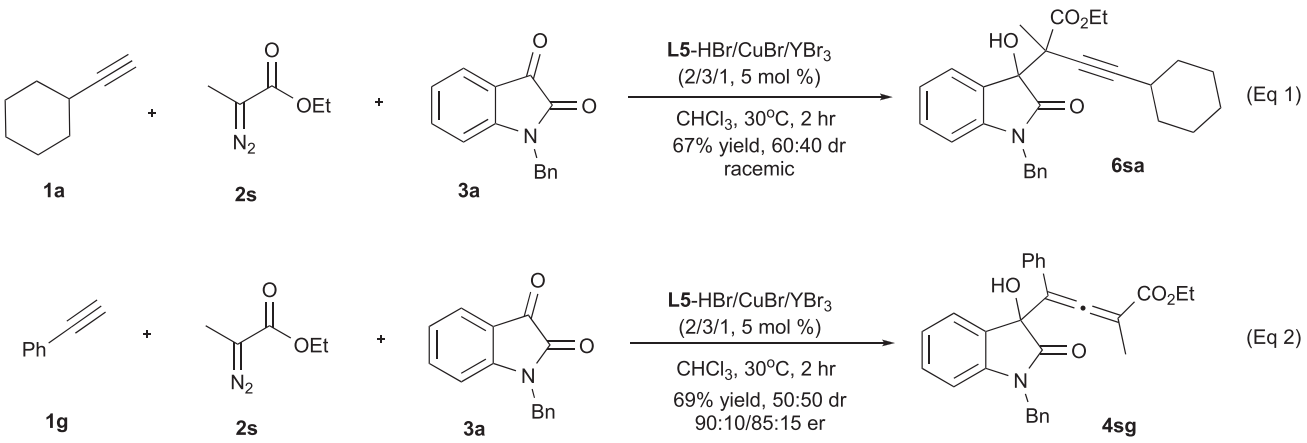


Figure 1. Reaction with α-Methyl-α-diazoesters

the desired cyclic allenoate **4t**, albeit the yield and stereoselectivity were not satisfied (Figure 2; see Table S15, Scheme S65, and Figures S108–S109 for details). Other nucleophiles, such as 1H-indene-1,2,3-trione and ethyl 3,3,3-trifluoro-2-oxopropanoate, underwent the AMCRs with cyclohexyl acetylene **1a** and phenyl α-diazoester **2h** to give the corresponding carbinol allenoate products in moderate to good yields but without stereocontrol (see Schemes S2 and S62–S64 and Figures S102–S107 for details). Nevertheless, the reaction of ethyl 2-oxoacetate yielded the carbinol pent-3-ynoate product via trapping of alkynoate-copper intermediate (Scheme S2).

We next conducted an exploration of the scope of terminal alkynes in AMCRs under optimized reaction conditions. Table 4 shows the results of alkyl- and aryl-substituted alkynes (see Table S13, Schemes S1 and S45–S61, and Figures S68–S101 for details). A range of alkyl acetylenes including cyclic and acyclic groups were tolerated and, generally, high levels of reaction efficiency and good enantioselectivities were observed (Table 4, entries 1–4; 90%–98% yield, 88:12 to 95:5 er). A similar result could be obtained from the reaction of propargyl (*S*)-citronellyl ether **1f** (Table 4, entry 5). The alkyne **1g** bearing methylcarbamate substituent underwent the reaction in good yield and moderate stereoselectivity, possibly because of the inherent H-bonding interaction with the guanidinium ligand (Table 4, entry 6). For the terminal alkyne **1h** with an acetal group complete reactions occurred, giving a mixture of the desired product **4h** in good diastereo- and enantioselectivity (49% yield, 96:4 er, and 80:20 dr) and the corresponding H-trapping allenoate **5hh** (Table 4, entry 7; 38% yield, racemate). The alkenyl group was perfectly tolerated to give the desired AMCR product **4i** in 90% yield, 97:3 er, and 80:20 dr, and a cyclopropanation by-product was not observed (Table 4, entry 8). Pleasingly, aryl acetylenes also performed well, giving the desired diaryl-substituted allenoates **4j–4q** in 87%–97% yield, 93:7 to 97:3 er, and 76:24 to 88:12 dr (Table 4, entries 9–16). Therefore, this AMCR is a good complement to the alleno-addition process[46–48] and alkynylogous Mukaiyama aldol strategy.[49]

How did the MCR reaction perform in this catalytic system? Our mechanistic hypothesis (Scheme 2C) was supported by control experiments (see Schemes 3 and S4 for details). Indeed, trisubstituted allenoate **5ha** was obtained in 98% yield and 68:32 er under the standard catalytic condition in the absence of isatin. When **5ha** was subjected to reaction with isatin **3a** assisted by various catalyst components, even in the presence of guanidine **L5**/CuBr/YBr_3 for 12 hr, no targeted

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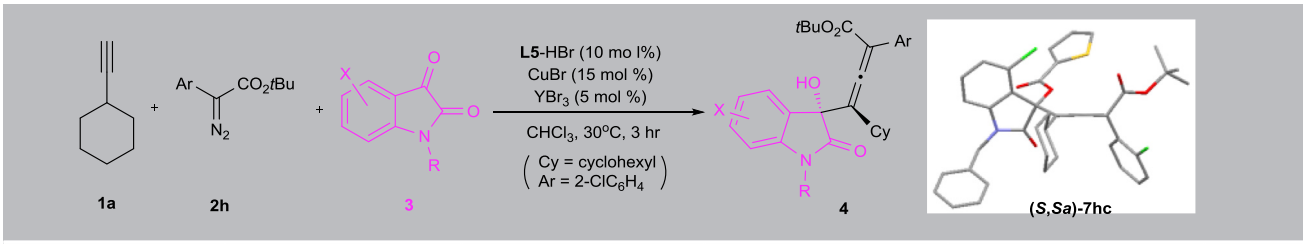
Table 3. Substrate Scope for Isatins



Entry[a]	X	R	Yield (%)	er	dr
1	4-F	Bn	94 (4hb)	96:4 (*S*,*Sa*)	95:5
2	4-Cl	Bn	95 (4hc)	96:4 (*S*,*Sa*)	95:5
3[b]	4-Cl	Bn	91 (4hc)	96:4 (*S*,*Sa*)	95:5
4	4-Br	Bn	96 (4hd)	96:4 (*S*,*Sa*)	95:5
5	5-Br	Bn	97 (4he)	92:8	85:15
6	6-Br	Bn	96 (4hf)	94:6	80:20
7	7-Br	Bn	96 (4hg)	91:9	64:36
8	5-Me	Bn	96 (4hh)	98:2	88:12
9	5-MeO	Bn	96 (4hi)	97:3	86:14
10	6-MeO	Bn	88 (4hj)	98:2	90:10
11	5,7-Me_2	Bn	97 (4hk)	98:2	84:16
12	H	Me	98 (4hl)	93:7	82:18
13	H	PMB	98 (4hm)	98:2	89:11
14	H	$Ph(CH_2)_2$	98 (4hn)	98:2	85:15
15	H	H or Ts	ND	–	–

ND, not determined.

[a]Unless otherwise noted, the reactions were carried out on 0.10 mmol scale under the reaction condition of entry 11 in Table 1 for 3 hr.

[b]The reaction was carried out on 2.0 mmol scale.

tetrasubstituted allenoate **4ha** was detected. These results indicate that the process in this case is different from the previous reactions using trisubstituted allenoates as the reactants.[46–48] Moreover, in view of the observation of pentynoate product **6sa** (Figure 1, equation 1) and the desired carbinol allenoates **4**, the formation of alkynoate-copper species from the C–H insertion and 1,3-copper shift into allenoate-Cu(I) intermediate are possible. The low er value of **5ha** implies that the enantio- and diastereoselectivities in AMCRs are influenced by the interaction of isatin with the guanidine. The guanidinylated amides **L5** might act as multifunctional ligands: the CN_3 unit of **L5** interacts with copper salt to enable the formation of allenoate-copper intermediate, and sulfonamide unit bonds the isatin via intramolecular H-bond (see Figure S4 and Scheme S6 for details). The diastereo- and enantioselective addition reaction results in the formation of the desired product with axial chirality and tertiary alcoholic center. The latter nucleophilic addition

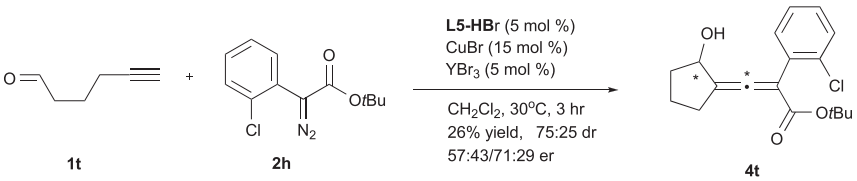


Figure 2. Reaction of Aldehyde in an Intramolecular Manner

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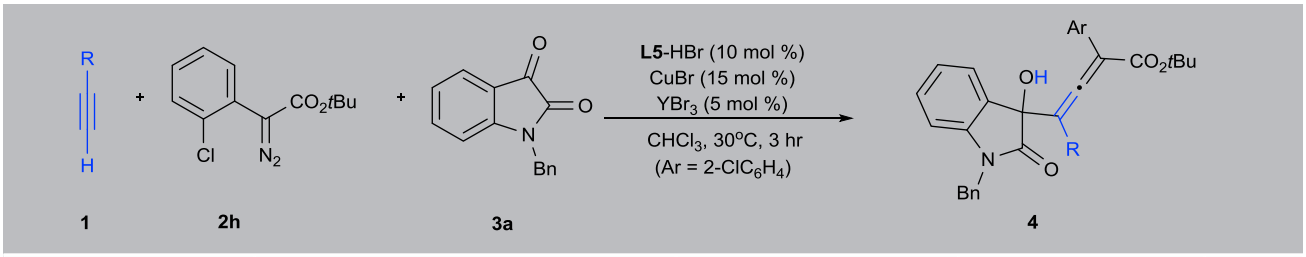
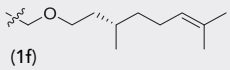
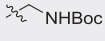
Table 4. Substrate Scope for Terminal Alkynes



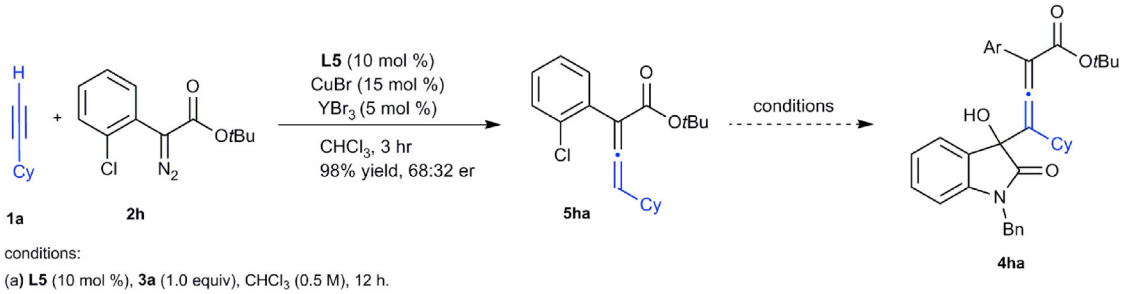
1 **2h** **3a** **4**

Entry[a]	R	Yield (%)[b]	er[c]	dr[d]
1	cyclopentyl (**1b**)	90 (**4b**)	95:5	84:16
2	Bn (**1c**)	98 (**4c**)	90:10	67:33
3	$BnCH_2$ (**1d**)	98 (**4d**)	88:12	67:33
4	*n*-$C_{10}H_{21}$ (**1e**)	98 (**4e**)	90:10	69:31
5	 (**1f**)	82 (**4f**)	91:9	70:30
6	 (**1g**)	81 (**4g**)	84:16	64:36
7[e]	 (**1h**)	49 (**4h**)	96:4	80:20
8	1-cyclohexenyl (**1i**)	90 (**4i**)	97:3	80:20
9	C_6H_5(**1j**)	94 (**4j**)	97:3	84:16
10	2-FC_6H_4 (**1k**)	88 (**4k**)	93:7	76:24
11	3-FC_6H_4 (**1l**)	87 (**4l**)	94:6	78:22
12	3-MeC_6H_4 (**1m**)	92 (**4m**)	97:3	87:13
13	2-$MeOC_6H_4$ (**1n**)	90 (**4n**)	96:4	85:15
14	3-$MeOC_6H_4$ (**1o**)	96 (**4o**)	96:4	88:12
15	4-$MeOC_6H_4$ (**1p**)	94(**4p**)	97:3	84:16
16	4-EtC_6H_4 (**1q**)	97 (**4q**)	97:3	85:15

[a]Unless otherwise noted, all reactions were carried out with **L5**-HBr (10 mol %), CuBr (15 mol %), YBr_3 (5 mol %), **1** (0.10 mmol), **2h** (0.15 mmol), and **3a** (0.10 mmol) in CH_3Cl (0.2 mL) at 30°C for 3 hr.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]Determined by NMR.
[e]Tri-substituted allene by-product **5hh** via H-trapping pathway was obtained in 38% yield and 50:50 er.

step is the enantioselection-determining step, and the C–H insertion is the diastereoselection-determining step, but the two stereocontrol factors will influence one another.

The fact that combination of **L5**/CuBr/YBr_3 is highly reactive for the generation of allenoate **5ha** from alkyne **1a** and α-diazoester **2h** (Scheme 3) also reveals that Y(III) salt benefits the C–H insertion step rather than the electrophilic addition of isatin through a Lewis acid activation manner, given the fact that C–H insertion of aromatic α-diazoester to terminal alkynes required CuCl as high as 90 mol % in our previous study.[19] Thus, the assistance of another acid might address the drawback of a large amount of copper salt used in the asymmetric C–H insertion step. Pleasingly, it was true that the loading of CuCl could be greatly reduced in the C–H insertion by adding 5 mol % of YCl_3 instead (see Tables S5–S7 for details).



conditions:

(a) **L5** (10 mol %), **3a** (1.0 equiv), $CHCl_3$ (0.5 M), 12 h.

(b) **L5-HBr** (10 mol %), **3a** (1.0 equiv), $CHCl_3$ (0.5 M), 12 h.

(c) **L5** (10 mol %), CuBr (15 mol %), YBr_3 (5 mol %), **3a** (1.0 equiv), $CHCl_3$ (0.5 M), 12 h.

(d) **L5-HBr** (10 mol %), CuBr (15 mol %), YBr_3 (5 mol %), **3a** (1.0 equiv), $CHCl_3$ (0.5 M), 12 h.

Scheme 3. Control Experiments

The enantioselectivity of the C–H insertion of α-diazoester to alkyne **1r** was not affected and the reaction efficiency improved (Table 5, entry 2 versus entry 1). We also noticed that long-time stored YCl_3 was superior to newly purchased YCl_3, indicating that moisture might cause the hydrolysis of YCl_3, generating a trace amount of HCl to assist the reaction (Table 5, entry 2 versus entry 3). Considering the performance of guanidinium halo salt in comparison with the corresponding guanidine, we wondered whether a catalytic amount of hydrogen halide could work. Thus, various additives were tested as shown in Table 5. When the YCl_3/HCl combination was introduced into the catalytic system, the yield increased and the reaction time shortened (Table 5, entry 4). Furthermore, it was extremely interesting that using HCl as the sole additive could also improve the efficiency of the reaction (Table 5, entries 5 and 6). When the amount of HCl increased, a similar result with regard to the HCl/YCl_3 system was obtained. In the presence of **L4**-HCl/CuCl/HCl (1:2:1, 5 mol %), the asymmetric C–H insertion reaction occurred rapidly, and the targeted allenoate **5br** was given in 90% yield and 96:4 er (Table 5, entry 6). We also confirmed the critical role of guanidine **L4** in that only a trace amount of the C–H insertion product was detected without it, revealing an obvious ligand-accelerating effect[58] (Table 5, entry 7). Other control experiments using *N*-Boc-protected amino amide **L10** and amino amide **L11** instead of **L4** resulted in poor yield and enantioselectivity (Table 5, entries 8 and 9), indicating the unique characteristic of the guanidine unit.

We tried to determine the X-ray crystal structure of the catalyst but without a positive result. However, it was found that the addition of **L4**, **L4**-HCl, or **L11** could accelerate the dissolution of CuCl in tetrahydrofuran with obvious color change, whereas *N*-Boc-protected **L10** did not work (see Figure S1 for details). The NMR study of **L4**-HCl combined with CuCl showed obvious changes in chemical shift in comparison with the sole **L4**-HCl (see Scheme S7 and Figures S128–S140 for details). This implied the coordination of guanidinium salt with the copper salt,[59] and the developed compounds represent a type of guanidinylated ligand for asymmetric catalysis. Furthermore, the role of HX or YX_3 (X = Br, Cl) is proposed to interact with the basic nitrogens of the guanidine unit of the ligand, which belongs to the concept of combined acids.[51–53] The performance of **L4**-HCl/CuCl/HCl or **L4**-HCl/CuCl/YCl_3 is similar to cationic oxazaborolidine catalyst (Corey's BLAs)[52] and Corey-Bakshi-Shibata catalyst (known as CBS catalyst, a type of LLAs),[53] respectively. This hypothesis was supported by the NMR study of **L4**-HCl/CuCl, **L4**-HCl/CuCl/HCl, and **L4**-HCl/CuCl/YCl_3 catalytic systems. A slight chemical shift is detected in ^{1}H NMR and ^{13}C NMR spectra along with the addition of HCl and YCl_3 (see Scheme S7 for details). Although the actual coordination mode of the

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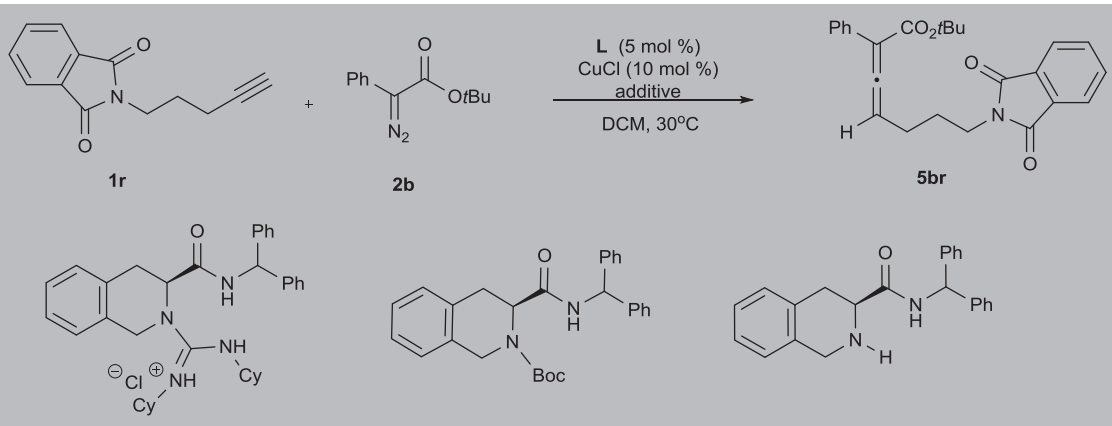
Table 5. Optimization of the Reaction Conditions of C–H Insertion Reactions



Entry[a]	L	Additive (mol %)	Conversion of 2 (%)[b]	Yield (%)[b]	er[c]
1	L4-HCl	–	35	31	97:3
2[d]	L4-HCl	YCl_3 (5)	100	85	97:3
3[e]	L4-HCl	YCl_3 (5)	47	42	96:4
4[e,f]	L4-HCl	YCl_3 (5) HCl (2.5)	100	99	96:4
5[e]	L4-HCl	HCl (2.5)	68	59	96:4
6[e,f]	L4-HCl	HCl (5)	100	90	96:4
7[e]	–	YCl_3 (5) HCl (2.5)	84	4	–
8	L10	HCl (5)	82	6	50:50
9	L11	HCl (10)	100	26	55:45

[a]All reactions were carried out with **L4**-HCl (5 mol %), CuCl (10 mol %), and YCl_3 (0–5 mol %), HCl (2.5–10 mol %), **1r** (0.10 mmol), and **2b** (0.12 mmol) in CH_2Cl_2 (0.5 mL) at 30°C for 2.5 hr. HCl (2.5 mol %: aq. 0.5 M, 5 μL); (5 mol %: aq. 1.0 M, 5 μL); (10 mol %: aq. 1.0 M, 10 μL).
[b]Determined by NMR using CH_2Br_2 as an internal standard.
[c]Determined by chiral HPLC.
[d]Long-time stored YCl_3 was used.
[e]Newly purchased YCl_3 was used.
[f]The reaction finished in 1 hr.

guanidinylated ligands remained unclear, the study is ongoing (see Figures S2 and S3 for proposed catalyst structures).

On the basis of this observation, we updated the asymmetric catalytic C–H insertion reaction of α-diazoesters. The substrate scope of various α-aryl α-diazoesters with the optimal **L4**-HCl/CuCl/HCl catalytic system is listed in Table 6 (see Table S14, Schemes S66–S72, and Figures S110–S123 for details). The desired allenoates **5** were given in good yields (86%–94%) and enantioselectivities (94:6 to 97:3 er), albeit the amount of HCl varied depending on the electronic nature of the substituents. Taking advantage of combined acids, the efficiency of guanidinylated copper complex was greatly improved with excellent maintained asymmetric environment.

We next extended the combined acids to the AMCRs to improve the reaction efficiency of some inert α-diazoesters (see Tables 7, S10, and S11 for details). It is no surprise to question whether hygroscopic property of YBr_3 will affect the

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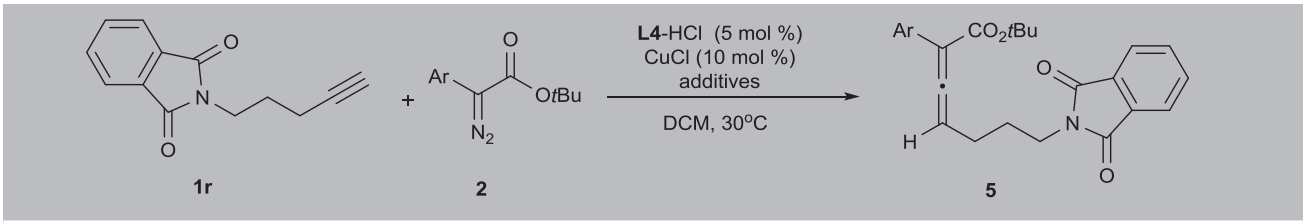
Table 6. Asymmetric C–H Insertion Reactions by the Combined-Acid System



Entry[a]	2: Ar	aq. HCl	Yield (%)[b]	er[c]
1	**2b**: C_6H_5	1.0 M	88 (**5br**)	96:4
2	**2c**: 2-MeC_6H_4	3.0 M	87 (**5cr**)	94:6
3	**2d**: 3-MeC_6H_4	1.0 M	86 (**5dr**)	95:5
4[d]	**2e**: 4-MeC_6H_4	1.0 M	84 (**5er**)	95:5
5	**2f**: 2-FC_6H_4	3.0 M	90 (**5fr**)	97:3
6	**2o**: 4-ClC_6H_4	3.0 M	94 (**5or**)	95:5
7	**2p**: 4-BrC_6H_4	4.0 M	99 (**5pr**)	94:6

[a]**L4**-HCl (5 mol %), CuCl (10 mol %), and aq. HCl (x M, 5 μL), **1r** (0.10 mmol), and **2** (0.12 mmol) in CH_2Cl_2 (0.5 mL) at 30°C for 1 hr.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]CuCl (5 mol %) was used.

reaction in view of the positive influence of HCl in a two-component reaction (Table 5). Results in entries 2 and 3 showed that both anhydrous and long-time stored YBr_3 greatly accelerated the reaction, as did HBr as the additive (Table 7, entries 4–5). Nevertheless, YBr_3 was more efficient than HBr in AMCR. Superacid[51] combination of YBr_3/HBr could further increase the reaction activity without loss of the stereoselectivity. For the reaction of ethyl 2-diazo-2-phenylacetate **2b′**, significant improvement of yield was observed, whereas the amount of CuBr and reaction time was halved (Table 7, entry 6; versus Table 2, entry 1). The rise in the reactivity via additives was also useful for the reactions of α-diazoester **2d** and **2m** (Table 7, entries 7 and 8; versus Table 2, entries 4 and 13). The NMR study also suggested the interaction of the additives with **L5**-HBr/CuBr (see Scheme S8 and Figures S141–S152 for details). The counterions of the acids might have an influence on the acidity of the catalyst. In this sense, the involvement of Lewis acid (YBr_3)- or Brønsted acid (HBr)-assisted Lewis acid system (**L5**-HBr/CuBr) might be speculated for this AMCR although the main role of the copper center is to generate copper-carbene intermediate instead of a Lewis acid (see Figure S4 for the proposed mechanism).

In summary, the catalytic asymmetric and direct synthesis of tetrasubstituted allenoates through AMCRs of α-diazoesters with terminal alkynes and isatins was realized. A wide range of tetrasubstituted allenoates can be obtained in one pot with good to excellent yields and good chemo-, enantio-, and diastereoselectivities. The results confirmed the existence of allenoate-Cu(I) intermediates in C–H insertion of α-diazoesters. The use of a multifunctional chiral guanidinium salt ligand led to the success of Cu(I)-involved asymmetric MCRs of diazo compounds. Additionally, the reactivity of both C–H insertion of alkynes and MCRs has benefited greatly from the combined-acid strategy. The unique multi-nitrogen structure of guanidine provides variable opportunity to form designer acid catalysts. Further efforts are under way to illuminate the role of catalytic components in this route and optimize the reaction conditions for the enantioselective trap of the alkynoate intermediates.

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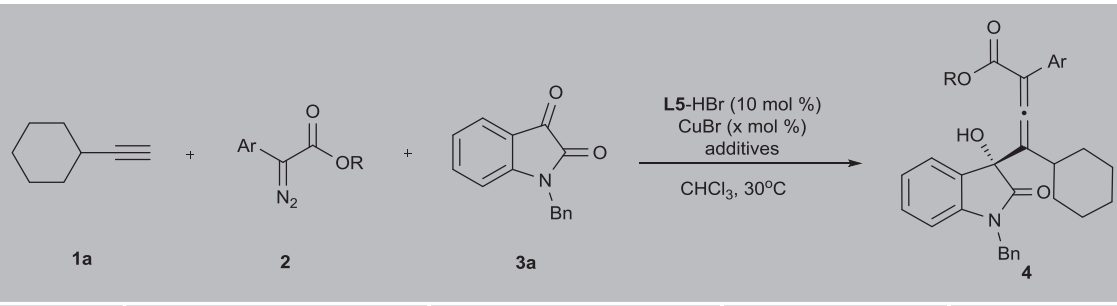
Table 7. Asymmetric Multicomponent Reactions by the Combined-Acid System



Entry[a]	2: Ar/R	Additives (mol %)	Yield (%)[b]	er[c]	dr[d]
1	**2a**: 1-naphthyl/Et	–	53 (**4aa**)	98:2	80:20
2	**2a**: 1-naphthyl/Et	YBr_3 (5)	94 (**4aa**)	98:2	80:20
3[b]	**2a**: 1-naphthyl/Et	YBr_3 (5)	94 (**4aa**)	98:2	80:20
4	**2a**: 1-naphthyl/Et	HBr (12.5)	60 (**4aa**)	98:2	80:20
5	**2a**: 1-naphthyl/Et	HBr (25)	84 (**4aa**)	98:2	80:20
6[c]	**2b′**: C_6H_4/Et	YBr_3 (10) HBr (37.5)	73 (**4b′a**)	95:5	80:20
7[d]	**2d**: 3-MeC_6H_4/*t*Bu	YBr_3 (5) HBr (12.5)	90 (**4da**)	95:5	83:17
8[d]	**2m**: 2-naphthyl/*t*Bu	YBr_3 (5) HBr (12.5)	89 (**4ma**)	94:6	83:17

[a]Unless otherwise noted, **L5**-HBr (10 mol %), CuBr (15 mol %), YBr_3 (0–5 mol %), HBr (12.5–37.5 mol %; 2.5–7.5 M, 5 μL), **1a** (0.10 mmol), **2** (0.15 mmol), and **3a** (0.10 mmol) in CH_3Cl (0.2 mL) at 30°C for 8 hr. Isolated yield. er determined by HPLC; dr determined by ^1H NMR.
[b]Newly purchased YBr_3 was used instead and the reaction was carried out in a glovebox.
[c]CuBr (30 mol %) for 4 hr.
[d]Reacting for 0.5 hr.

EXPERIMENTAL PROCEDURES

Detailed experimental procedures are provided in the Supplemental Information.

DATA AND SOFTWARE AVAILABILITY

Crystallographic data have been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1582751.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, 156 figures, 15 tables, 74 schemes, and 1 data file and can be found with this article online at https://doi.org/10.1016/j.chempr.2018.04.012.

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AUTHOR CONTRIBUTIONS

Methodology, Y.T. and X.L.; Investigation, Y.T., J.X., and J.Y.; Writing – Original Draft, Y.T.; Writing – Review & Editing, X.L., L.L., and X.F.; Supervision, X.L.

DECLARATION OF INTERESTS

There are no competing interests.

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