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To be cited as: *Chem. Eur. J.* 10.1002/chem.201604962

Link to VoR: http://dx.doi.org/10.1002/chem.201604962

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Enantioselective Formal C-H Conjugate Addition of Acetanilides to β-Substituted Acrylates by Chiral Iridium Catalysts

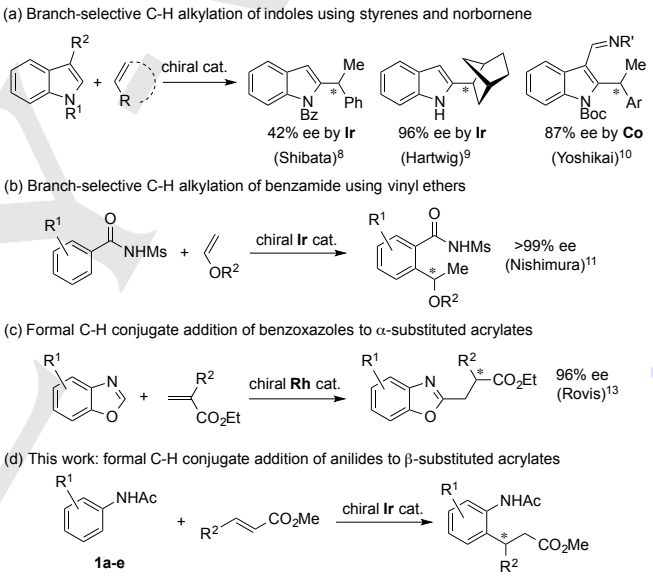
Takanori Shibata,*[a],[b] Masamichi Michino,[a] Hisaki Kurita,[a] Yu-ki Tahara,[a] and Kyalo Stephen Kanyiva[c]

Dedication ((optional))

Abstract: *The Ir-catalyzed enantioselective reaction of substituted acetanilides with β-substituted α,β-unsaturated esters gave chiral 3,3-disubstituted propanoates in high yield with good to excellent enantiomeric excess (up to 99% ee). The present transformation initiated by sp^2 C-H bond activation is the first example of enantioselective formal C-H conjugate addition to β-substituted α,β-unsaturated carbonyl compounds. The starting materials are commercially available and/or readily accessible.*

The direct conversion of ubiquitous C-H bonds is an ideal transformation in organic synthesis.[1] In particular, a catalytic and enantioselective reaction initiated by C-H bond cleavage is a target of aggressive research in asymmetric synthesis. A clear-cut approach to the creation of central chirality is the enantioselective activation of a secondary sp^3 C-H bond, and Yu reported the chiral Pd-catalyzed sp^3 C-H bond activation of cyclopropanes with boron reagents using a carbamoyl directing group.[2,3] We previously reported the chiral Ir-catalyzed sp^3 C-H alkylation of alkyl amines with various alkenes using a pyridyl directing group for the preparation of chiral secondary amines.[4a,b] We further used this enantioselective C-H alkylation strategy for the synthesis of γ-amino acid derivatives with the use of γ-lactams as substrates.[4c]

Another attractive protocol for the creation of central chirality is the hydroarylation of an alkene initiated by sp^2 C-H bond activation. Since Murai's pioneering work,[5] chiral Rh-catalyzed intramolecular reactions have been comprehensively studied by Bergman and Ellman: hydroarylation of various alkenes generated stereogenic centers.[6,7] Regarding the intermolecular reaction, the branch-selective C2 C-H alkylation of an indole is a typical strategy: the first example of the Ir-catalyzed C-H alkylation of *N*-benzylindole with styrene[8] was followed by the Ir-catalyzed alkylation with norbornene[9] and the Co-catalyzed C-H alkylation of 3-iminoindole[10] (Scheme 1a). For compounds other than indole derivatives, Nishimura recently reported the Ir-catalyzed branch-selective C-H alkylation of benzamide derivatives with various vinyl ethers (Scheme 1b).[11,12] Another approach involved formal C-H conjugate addition of benzoxazoles to α-substituted acrylates.[13] Against this background, we report here an enantioselective formal C-H conjugate addition to β-substituted α,β-unsaturated esters (Scheme 1d). The Ir-catalyzed enantioselective reaction of acetanilides with crotonates gives chiral *ortho*-phenylene-tethered δ-amino acid derivatives.



Scheme 1. Enantioselective intermolecular C-H alkylation with alkenes initiated by sp^2 C-H bond activation

Although many examples of sp^2 C-H alkylation with alkenes have been reported,[1,14] there are few examples with electron-deficient olefins, such as α,β-unsaturated carbonyl compounds, which are fascinating because of their potential to provide synthetically useful alkylated compounds.[15,16] Among them, the reactions of α,β-unsaturated esters, namely formal C-H conjugated addition, has recently been a hot topic.[17] However, there is no example of an enantioselective variant to β-substituted α,β-unsaturated carbonyl compounds.

We chose (3'-methyl)acetanilide (**1a**) and (*E*)-methyl crotonate (**2a**) as model substrates and conducted the reaction in the presence of various chiral Ir catalysts, which were prepared *in situ* from $[Ir(cod)_2]OTf$ and chiral diphosphine ligands.[18] As a result, 2,3-bis(diphenylphosphino)butane (CHIRAPHOS) gave alkylated product **3aa** in good yield and ee, and 5,5'-

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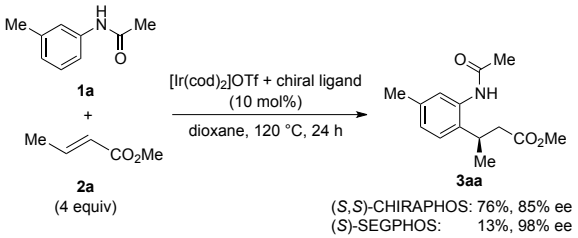
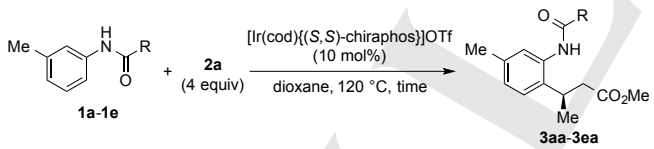
bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole (SEGPHOS) realized almost perfect enantioselectivity, albeit in low yield due to the low conversion of substrate **1a**.[19]



Scheme 2. Preliminary results of the enantioselective reaction of anilide **1a** with **2a**.

We next investigated the effect of an amide directing group using preliminarily prepared Ir-CHIRAPHOS catalysts, which were purified by column chromatography[20] (Table 1). In addition to propionamide **1b**, more bulky isobutyramide **1c** gave almost the same results as acetamide **1a** (entries 1-3). In contrast, the electronic effect was significant, and the reaction of phenylacetamide **1d** or trifluoroacetamide **1e** did not proceed at all (entries 4 and 5). We determined that acetamide **1a** could be used as a standard substrate. When we used a longer reaction time, the amide was completely consumed, and quantitative yield was achieved without a loss of ee (entry 6). Comparable results were obtained even under solvent-free conditions (entry 7). When exactly a stoichiometric amount of alkene **2a** was used, the yield was still high (entry 8). It is noteworthy that only 2 mol% of the catalyst achieved the quantitative yield without loss of ee (entry 9).

***Table 1*:** Screening of amide directing groups in the enantioselective reaction of anilides **1a**-**1e** with (*E*)-methyl crotonate (**2a**)

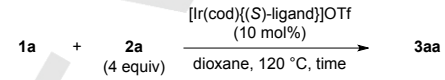


Entry	R	Time [h]	Yield [%]	*ee* [%]
1	Me (**1a**)	24	79 (**3aa**)	84
2	Et (**1b**)	24	66 (**3ba**)	81
3	*i*-Pr (**1c**)	24	76 (**3ca**)	81
4	Bn (**1d**)	24	NR	-
5	CF_3 (**1e**)	24	NR	-
6	Me (**1a**)	72	>99 (**3aa**)	85
7[a]	Me (**1a**)	72	>99 (**3aa**)	85
8[b]	Me (**1a**)	72	85 (**3aa**)	85
9[c]	Me (**1a**)	72	>99 (**3aa**)	85

[a] The reaction was conducted under the neat conditions. [b] Alkene **2a** (1 equiv) was used. [a] The chiral Ir catalyst (2 mol%) was used.

Since the enantioselectivity still had room for improvement, we further examined the reaction conditions using SEGPHOS analogues (Table 2). When we used the preliminarily prepared Ir-SEGPHOS catalyst, the yield remained low even under neat conditions (entries 1 and 2). Among SEGPHOS analogues, DIFLUORPHOS showed a drastic increase in conversion (entries 3-5), and the yield reached 50% under prolongation of the reaction time (entry 6). Two equivalent amounts of alkene **2a** gave comparable results.

Table 2: Screening of SEGPHOS analogues in the enantioselective reaction of anilide **1a** with **2a**.



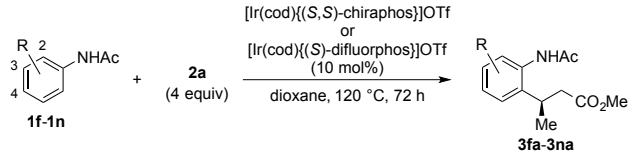
Entry	Ligand[a]	Time [h]	Yield [%]	*ee* [%]
1	SEGPHOS	24	22	97
2[b]	SEGPHOS	24	25	97
3	DM-SEGPHOS	24	16	98
4	SYNPHOS	24	16	95
5	DIFLUORPHOS	24	43	98
6	DIFLUORPHOS	72	50	97
7[c]	DIFLUORPHOS	72	48	97

[a] DM-SEGPHOS: 5,5'-bis[di(3,5-xylyl)phosphine]-4,4'-bi-1,3-benzodioxole, SYNPHOS: 6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin, DIFLUORPHOS: 5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole. [b] Under neat conditions. [c] Crotonate **2a** (2 equiv) was used.

We used cationic Ir–CHIRAPHOS or –DIFLUORPHOS catalyst to investigate the substrate scope of mono- and disubstituted acetanilides (Table 3). Regarding the 3 position, both electron-donating and –withdrawing groups were tolerable, and chiral *ortho*-phenylene-tethered δ-amino acids derivatives **3fa-3la** were obtained with good to excellent ee (entries 1-6). 3,4-Disubstituted acetanilides **1i** and **1j** were also transformed into the corresponding C-H alkylated products **3ia** and **3ja**, respectively (entries 7-9). The Ir–DIFLUORPHOS catalyst realized excellent ee, but resulted in low yield due to low conversion, except for (3'-methoxy)acetanilide (**1f**) (entry 2). The substituent at the 2 position had a significant effect: while the reaction of (2'-methyl)acetanilide (**1k**) with the Ir-CHIRAPHOS catalyst proceeded with high enantioselectivity (91% ee), that of (2'-chloro)acetanilide (**1m**) did not proceed at all (entries 10-13). When the parent acetanilide (**1n**) was subjected to the standard

conditions, the inseparable mixture of mono- and dialkylated products was obtained, but the selective formation of **3na** was achieved by the use of exactly a stoichiometric amount of alkene **2a** (entries 14 and 15).

Table 3: Substrate scope of substituted acetanilides **1** in the reaction with methyl crotonate (**2a**)

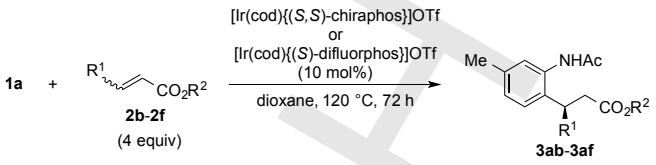


Entry	R	Ligand[a]	Yield [%]	*ee* [%]
1	3-OMe (**1f**)	**A**	90 (**3fa**)	84
2	3-OMe (**1f**)	**B**	60 (**3fa**)	98
3	3-Cl (**1g**)	**A**	89 (**3ga**)	81
4	3-Cl (**1g**)	**B**	11 (**3ga**)	96
5	3-CF_3 (**1h**)	**A**	62 (**3ha**)	78
6	3-CF_3 (**1h**)	**B**	12 (**3ha**)	94
7	3,4-Me_2 (**1i**)	**A**	98 (**3ia**)	85
8	3,4-Me_2 (**1i**)	**B**	16 (**3ia**)	98
9	3-Cl-4-Me (**1j**)	**A**	64 (**3ja**)	81
10	2-Me (**1k**)	**A**	88 (**3ka**)	91
11	2-MeO (**1l**)	**A**	85 (**3la**)	90
12	2-MeO (**1l**)	**B**	13 (**3la**)	97
13	2-Cl (**1m**)	**A**	ND	
14[b]	H (**1n**)	**A**	80 (**3na**)	86
15[b]	H (**1n**)	**B**	33 (**3na**)	96

[a] A: CHIRAPHOS, B: DIFLUORPHOS. [b] Alkene **2a** (1 equiv) was used.

Table 4 shows the reaction of **1a** with various β-substituted α,β-unsaturated esters **2b**-**2f**. The ester moiety greatly affected the results: while an isopropyl ester gave good results, a *tert*-butyl ester did not (entries 1-3). *n*-Pentyl and phenyl-substituted acrylates **2d** and **2e** were also good acceptors, and 3,3-disubstituted propanoates **3ad** and **3ae** were obtained with good to excellent ee (entries 4-7). Dimethyl fumarate (*E*)-**2f** also reacted with acetanilide **1a** to give chiral 2-arylsuccinate **3af** (entries 8 and 9). The reaction of dimethyl maleate gave **3af** in lower yield and ee, but the major enantiomer was the same as that derived from dimethyl fumarate (entry 10).

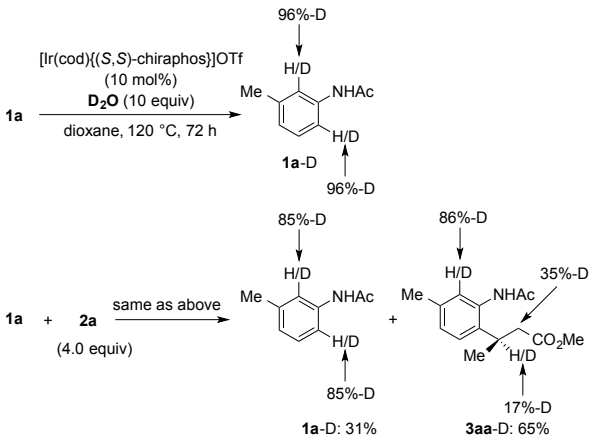
Table 4: Substrate scope of β-substituted α,β-unsaturated esters **2** in the reaction with acetamide **1a**



Entry	Alkene	Ligand[a]	Yield [%]	*ee* [%]
1	Me, CO_2(*i*-Pr) **2b**	**A**	>99 (**3ab**)	85
2		**B**	72[b] (**3ab**)	97
3	Me, CO_2(*t*-Bu) **2c**	**A**	ND	-
4	*n*-C_5H_{11}, CO_2Me **2d**	**A**	88 (**3ad**)	80
5		**B**	41 (**3ad**)	98
6	Ph, CO_2Me **2e**	**A**	78 (**3ae**)	80
7		**B**	31 (**3ae**)	99
8	MeO_2C, CO_2Me (*E*)-**2f**	**A**	51 (**3af**)	80
9		**B**	39 (**3af**)	99
10	CO_2Me, MeO_2C (*Z*)-**2f**	**A**	34 (**3af**)	73

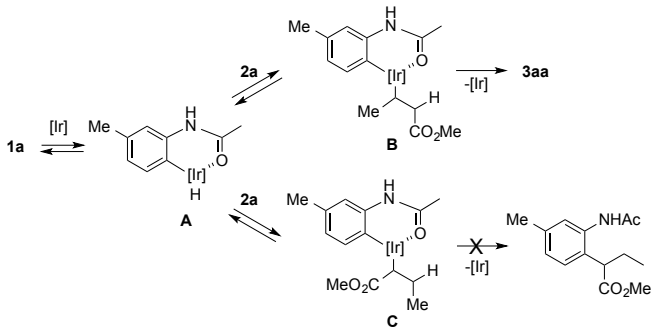
[a] A: CHIRAPHOS, B: DIFLUORPHOS. [b] NMR yield.

As a preliminary study of the reaction mechanism, the reaction of **1a** was conducted in the presence of D_2O (Scheme 3). Under alkene-free conditions, excellent H/D exchange occurred at both *ortho* positions of the amide group, which means that C-H bond cleavage is not regioselective. In the reaction with alkene **2a**, both the expected α-position and the β-position with respect to the ester moiety of product **3aa** were partly deuterated.



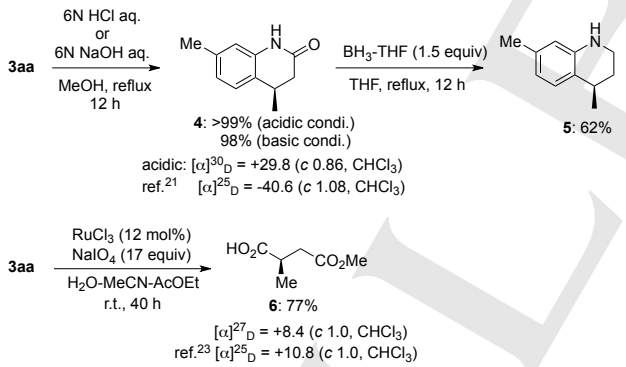
Scheme 3. Reaction of **1a** in the presence of D_2O without or with alkene **2a**

Based on the above results, we proposed the reaction mechanism (Scheme 4). Amide-directed sp^2 C-H bond cleavage gives iridium hydride species **A**. Subsequent hydrometalation to crotonate **2a** provides intermediates **B** and **C**. The first two steps are reversible. Final reductive elimination selectively proceeds from **B**, not from **C**, to give product **3aa**, and it is an irreversible step.[3]



Scheme 4. Proposed mechanism of the reaction of **1a** with **2a**

The obtained products can be useful synthetic intermediates (Scheme 5). Both acidic and basic hydrolysis of **3aa** readily afforded the known compound chiral δ-lactam **4**.[21] Subsequent reduction gave chiral tetrahydroquinoline **5**.[22] In contrast, **3aa** was transformed into (*R*)-(+)-2-methylsuccinic acid 4-methyl ester (**6**)[23] by RuO_4 oxidation.[24]



Scheme 5. Synthetic transformations of alkylated product **3aa**

In summary, we have demonstrated a new pattern of catalytic and enantioselective synthesis initiated by C-H bond activation. The reaction of substituted anilides and β-substituted acrylates, both of which are commercially available and/or readily accessible, proceeded to give a variety of chiral δ-amino acid derivatives with high to excellent ee. Further studies on enantioselective formal C-H conjugate addition are underway in our laboratory.

Acknowledgements

This work was supported by JST, ACT-C, Japan and Waseda University Grant for Special Research Projects. We are grateful to Umicore for generous supports in $[IrCl(cod)]_2$ supply.

Keywords: C-H alkylation • conjugate addition • enantioselective • iridium

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[18] Data for chiral ligand screening is listed in supporting information.

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10.1002/chem.201604962

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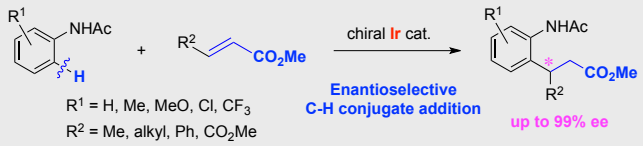

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