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Nickel(II)-Catalyzed Enantioselective α-Vinylation of β-Keto Amides/Esters with Hypervalent Iodine Salts

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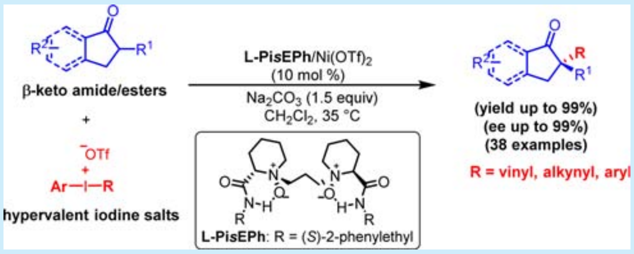
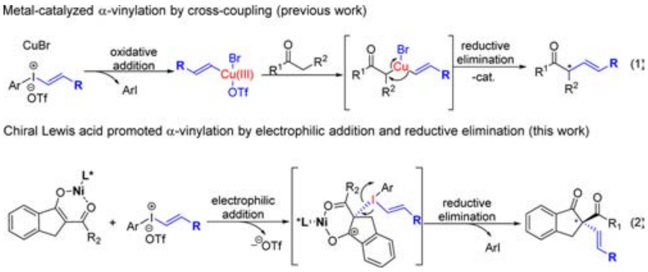
Supporting Information

ABSTRACT: The enantioselective α-vinylation of β-keto amides/esters using hypervalent iodine salts has been accomplished via a chiral *N*,*N*′-dioxide−nickel(II) complex promoted electrophilic addition and reductive elimination process. A wide range of vinyl-substituted all-carbon quaternary β-keto amides/esters were obtained in high yields and ee values (up to 99% yield and 99% ee). Moreover, the catalytic system has been applied to the enantioselective alkynylation/arylation of β-ketoamides with good results.



The catalytic asymmetric α-vinylation of carbonyl compounds provides efficient access to optically active vinyl derivatives that are widely distributed among medicinal agents and valuable building blocks for various transformations.[1] Some efforts have been devoted to the development of the transition-metal-catalyzed coupling of enolates with vinyl halides/boronic acids or organometallic reactants.[2,3] In comparison to the traditional vinyl reagents, vinyliodonium salts as highly activated species are more attractive due to their selectivity, low toxicity, and high stability.[4] Although significant progress of enantioselective α-arylation with hypervalent iodine salts has been achieved,[5] catalytic asymmetric α-vinylation is still rare.[6] The group led by MacMillan described the enantioselective α-vinylation of aldehydes using vinyliodonium triflate via the synergistic combination of copper and chiral amine catalysis.[6] The reaction mechanism involves a Cu(III)−vinyl intermediate followed by reductive elimination (Scheme 1, eq 1).[6,7] Recently, our laboratory introduced a new asymmetric catalytic strategy for α-arylation of oxindoles with iodonium salts via an electrophilic addition and rearrangement process.[8] Based on our long-term endeavor in the development of chiral catalysts stemming from metal/*N*,*N*′-dioxide complexes[9a−c] and previous studies of vinyliodonium salts,[9d−f] we determined that this unique strategy might be applied the enantioselective α-vinylation of β-keto amides/esters with hypervalent iodine salts (Scheme 1, eq 2). The challenge of using the unsymmetrical hypervalent iodonium salts is how to accurately control the chemoselectivity so that the vinyl transfers onto the nucleophile rather than the aryl group.[8b,10] Herein, we describe a chiral Lewis acid catalyzed asymmetric α-vinylation β-keto amide/ester with hypervalent iodine salts. Excellent chemo- and enantioselectivities were achieved for a variety of vinyl-substituted all-carbon quaternary β-keto amides/esters under mild reaction conditions.

Scheme 1. α-Vinylation with Hypervalent Iodine Salts



Our investigation began with the α-vinylation of β-ketoamides **1a** and vinyliodonium triflate **2a** as the model reaction to optimize the reaction conditions. In the presence of K_2CO_3, investigation of different Lewis acids coordinated to ligand **L-PiPh** derived from (*S*)-pipecolic acid showed that only $Ni(OTf)_2$ gave promising enantioselectivity (Table 1, entry 3 vs entries 1 and 2). The following survey of the ligands coordinated with $Ni(OTf)_2$ showed that the ligand **L-PisEPh** bearing (*S*)-phenylethanamine exhibited superior results (86% yield, 89% ee; Table 1, entry 4). In addition, L-pipecolic acid derived **L-PisEPh** was superior to L-proline acid derived **L-PrsEPh** and L-ramipril-derived **L-RasEPh** in terms of the reactivities and enantioselectivities (entry 4 vs entries 5 and 6). A chiral match was found among the subunits in the ligands. The use of ligand **L-PirEPh** bearing the (*R*)-phenylethanamine resulted in dramatically reduced enantioselectivity and yield (Table 1, entry 7). Further survey of other bases showed that a slightly improved enantioselectivity (95% ee) was achieved using Na_2CO_3 as base (Table 1, entry 8). When the ratio of ligand and $Ni(OTf)_2$ was fixed to 1:1.2, the desired product **3aa** was generated in 99% yield and 97% ee (Table 1, entry 9).

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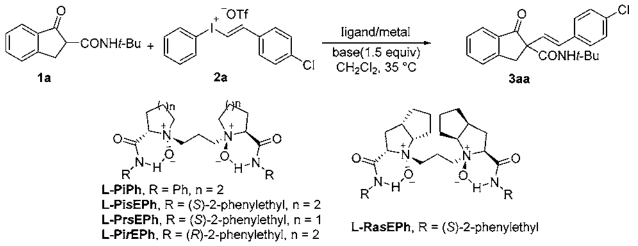
Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

L-PiPh, R = Ph, n = 2
L-PisEPh, R = (*S*)-2-phenylethyl, n = 2
L-PrsEPh, R = (*S*)-2-phenylethyl, n = 1
L-PirEPh, R = (*R*)-2-phenylethyl, n = 2

L-RasEPh, R = (*S*)-2-phenylethyl

entry	metal	ligand	base	yield[b] (%)	ee[c] (%)
1	CuBr	**L-PiPh**	K_2CO_3	56	0
2	$Sc(OTf)_3$	**L-PiPh**	K_2CO_3	33	6
3	$Ni(OTf)_2$	**L-PiPh**	K_2CO_3	44	22
4	$Ni(OTf)_2$	**L-PisEPh**	K_2CO_3	86	89
5	$Ni(OTf)_2$	**L-PrsEPh**	K_2CO_3	46	24
6	$Ni(OTf)_2$	**L-RasEPh**	K_2CO_3	47	41
7	$Ni(OTf)_2$	**L-PirEPh**	K_2CO_3	31	30[f]
8	$Ni(OTf)_2$	**L-PisEPh**	Na_2CO_3	90	95
9[d]	$Ni(OTf)_2$	**L-PisEPh**	Na_2CO_3	99	97
10[e]	$Ni(OTf)_2$	**L-PisEPh**	Na_2CO_3	99	95

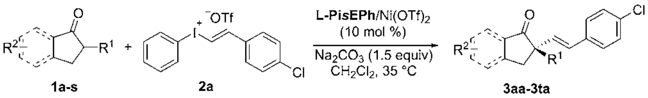
[a] The reaction was carried out with **1a** (0.1 mmol), metal/ligand (1:1; 10 mol %), base (0.15 mmol), and vinyliodonium triflate **2a** (0.12 mmol) in CH_2Cl_2 (1.0 mL) at 35 °C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **L-PisEPh**/$Ni(OTf)_2$ (1:1.2; 10 mol %). [e] **L-PisEPh**/$Ni(OTf)_2$ (1:1.2; 5 mol %). [f] The reverse of the enantioselectivity.

Notably, the catalyst loading could be decreased to 5 mol % and the yield maintained albeit with a slightly reduced ee value (Table 1, entry 10). The vinylated product **3aa** was unambiguously determined to be in the *R* configuration by X-ray analysis.[11]

With the optimized reaction conditions in hand, the substrate generality of the reaction was next surveyed. First, when a range of β-keto amides and esters were examined by reaction with vinyliodonium triflate **2a**, the reactions performed well, giving the corresponding α-vinylated β-ketoamides in 85−99% yields with 94−99% ee (**3aa**−**ha**) (Table 2, entries 1−8) and α-vinylated β-ketoesters in 78−98% yields with 94−99% ee (**3ia**−**pa**) (Table 2, entries 9−16), regardless of the electronic nature and the position of substituents on the aromatic ring of the indenone scaffold. Changing the ester group of the β-ketoesters from *tert*-butyl to adamantyl delivered the desired α-vinylated product **3qa** in 99% yield and 97% ee, which was similar to the results for **3ia**. Moreover, the β-ketoesters with simple saturated or unsaturated aliphatic rings were also tolerated, giving **3ra**−**sa** in moderate yields and high ee's. The 1-tetralone-derived β-ketoamide **1t** was also examined. However, the enantioselectivity and reaction activity decreased (**3ta**) (Table 2).

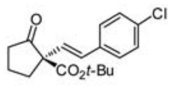
Next, we turned our attention to the scope of vinyliodonium triflates[12] (**3ab**−**ae**) (Scheme 2). Simple vinyliodonium triflate **2b** and electron-donating styryl-substituted vinyliodonium triflate **2c** could be transferred readily with excellent levels of enantiocontrol (96% ee) (**3ab**−**ac**) (Scheme 2). The alkyl-substituted vinyliodonium triflates, such as 3-phenylprop-1-en-1-yl and cyclohexyl, could also undergo this reaction smoothly, producing the desired adducts **3ad**−**ae** with good results (98−99% ee) (Scheme 2). In addition, this catalytic system was extended to the α-alkynylation reactions (**3af**−**ag**) (Scheme 2). When alkynyliodonium salts[13] **2f,g** were used as alkynylation reagents, though complicated reaction mixtures were observed, **3af** and **3ag** were still obtained in moderate yields with excellent enantioselectivities (98% ee).

Table 2. Substrate Scope of the Asymmetric α-Vinylation[a]

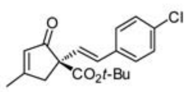


1a-s **2a** **3aa-3ta**

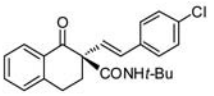
entry	R^1	R^2	**3**, yield[b] (%)	ee[c] (%)
1	CONH*t*-Bu	H	**3aa**, 99	97
2	CONH*t*-Bu	5-F	**3ba**, 97	97
3	CONH*t*-Bu	5-Cl	**3ca**, 99	96
4	CONH*t*-Bu	5-Br	**3da**, 90	96
5	CONH*t*-Bu	6-Cl	**3ea**, 90	94
6	CONH*t*-Bu	6-Me	**3fa**, 85	98
7	CONH*t*-Bu	6-OMe	**3ga**, 99	96
8	CONH*t*-Bu	5,6-OMe_2	**3ha**, 96	99
9	CO_2t-Bu	H	**3ia**, 95	97
10	CO_2t-Bu	5-F	**3ja**, 98	98
11	CO_2t-Bu	5-Cl	**3ka**, 85	98
12	CO_2t-Bu	5-Br	**3la**, 90	96
13	CO_2t-Bu	6-F	**3ma**, 78	94
14	CO_2t-Bu	6-Cl	**3na**, 92	95
15	CO_2t-Bu	6-Me	**3oa**, 90	99
16	CO_2t-Bu	4,5-OMe_2	**3pa**, 88	99
17	CO_2Ad	H	**3qa**, 99	97



3ra (55%, ee = 99%)



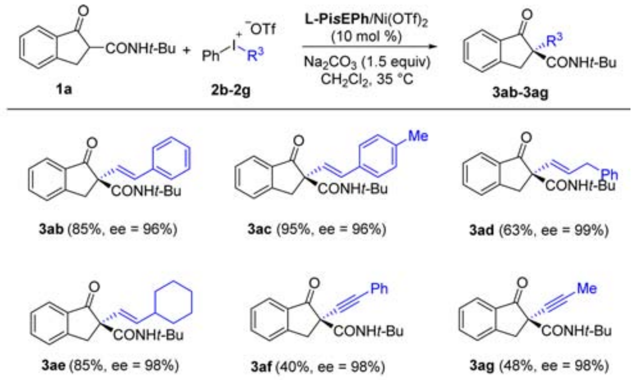
3sa (88%, ee = 99%)



3ta (59%, ee = 75%)

[a] All reactions were performed with **1** (0.1 mmol), **L-PisEPh**/$Ni(OTf)_2$ (1:1.2; 10 mol %), Na_2CO_3 (0.15 mmol), and vinyliodonium triflate **2a** (0.12 mmol) in CH_2Cl_2 (1.0 mL) at 35 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Scheme 2. Substrate Scope of the Asymmetric α-Vinylation/α-Alkynylation[a]



1a **2b-2g** **3ab-3ag**

3ab (85%, ee = 96%) **3ac** (95%, ee = 96%) **3ad** (63%, ee = 99%)

3ae (85%, ee = 98%) **3af** (40%, ee = 98%) **3ag** (48%, ee = 98%)

[a] All reactions were performed with **1a** (0.1 mmol), **L-PisEPh**/$Ni(OTf)_2$ (1:1.2; 10 mol %), Na_2CO_3 (0.15 mmol), and hypervalent iodine salts **2** (0.12 mmol) in CH_2Cl_2 (1.0 mL) at 35 °C for the indicated time.

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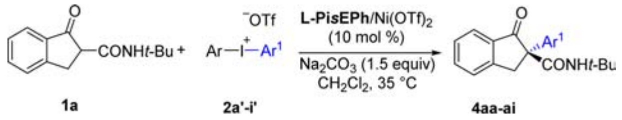
After investigation of the α-vinylation and alkynylation, we applied this catalyst system to α-arylation reactions (Table 3).

Table 3. Substrate Scope of the Asymmetric α-Arylation[a]



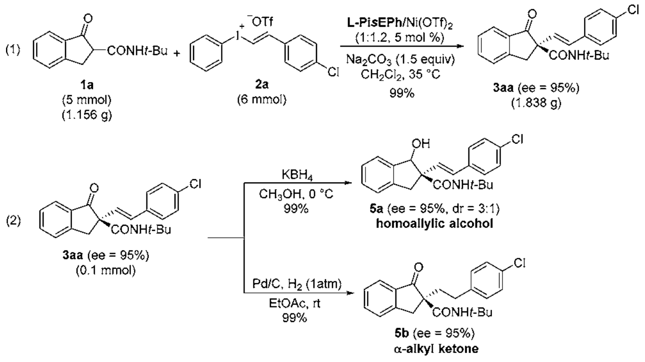
entry	Ar	Ar^1	**4**, yield[b] (%)	ee[c] (%)
1	Ph	Ph	**4aa**, 98	97
2	4-FC_6H_4	4-FC_6H_4	**4ab**, 99	93
3	4-ClC_6H_4	4-ClC_6H_4	**4ac**, 91	93
4	4-BrC_6H_4	4-BrC_6H_4	**4ad**, 99	95
5	4-MeC_6H_4	4-MeC_6H_4	**4ae**, 87	91
6	4-$tBuC_6H_4$	4-$tBuC_6H_4$	**4af**, 99	93
7	Mes	Ph	**4aa**, 98	95
8	Mes	3-FC_6H_4	**4ag**, 95	97
9	Mes	4-ClC_6H_4	**4ac**, 99	99
10	Mes	3-BrC_6H_4	**4ah**, 95	99
11	Mes	4-BrC_6H_4	**4ad**, 99	98
12	Mes	4-PhC_6H_4	**4ai**, 65	96

[a] All reactions were performed with **1** (0.1 mmol), **L-PisEPh**/$Ni(OTf)_2$ (1:1.2; 10 mol %), Na_2CO_3 (0.15 mmol), and hypervalent iodine compounds **2′** (0.12 mmol) in CH_2Cl_2 (1.0 mL) at 35 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

The symmetrical diaryliodonium triflates[14] containing electron-rich or electron-deficient aryl groups could be successfully employed in this context with high enantioselective levels (91–97% ee) and good yields (87–99%; Table 3, entries 1–6). Notably, the nonsymmetrical arylmesityl reagents[5d,e] including *meta*- and *para*-substituted aryl rings with diverse steric and electronic properties, could also be readily exploited (Table 3, entries 7–12). The arylated product **4aa** was unambiguously determined to be *R* configuration by X-ray analysis[11] (Table 3, entry 1).

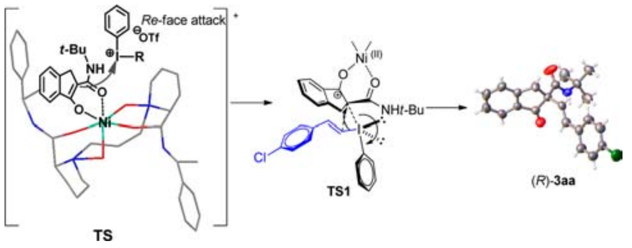
To show the utility of the current method, a gram-scale synthesis of 3-benzyl-3-aryloxindole **3aa** was carried out. In the presence of 5 mol % of catalyst, β-ketoamides **1a** (1.156 g, 5 mmol) reacted smoothly with vinyliodonium triflate **2a** (6 mmol), giving 1.838 g (99% yield) of the product **3aa** in 95% ee (Scheme 3, eq 1). The product **3aa** could be efficiently converted to homoallylic alcohol **5a** and α-alkyl ketone **5b** through reduction by using KBH_4 and Pd/C (Scheme 3, eq 2).

Scheme 3. Scaled-up Version of the Reaction and Further Transformations of the Product 3aa



Preliminary studies of the mechanism were carried out by HRMS experiments. The coordination of *N,N′*-dioxide **L-PisEPh** with $Ni(OTf)_2$ was confirmed by the ion peak at *m/z* 743.6519, corresponding to the intermediate $[Ni^{2+}$ + **L-PisEPh** + $TfO^-]^+$. Peaks at *m/z* 412.9337 and 974.9349 were assigned to $[Ni^{2+}$ + **L-PisEPh** + **1a**$]^{2+}$ and $[Ni^{2+}$ + **L-PisEPh** + **1a** + $TfO^-]^+$, respectively, which indicated the association of β-ketoamide to the metal center. Based on the experiments and previous studies,[8c,9] a possible transition-state model was proposed to elucidate the stereocontrol. As shown in Scheme 4, the enolate of β-ketoamides coordinated with the nickel(II) in a bidentate fashion using the oxygens of the dicarbonyl groups. Due to the severe steric effect and the decrease of the electronic-charge density on oxygen, the generation of an O–I bond or the isomerization of C–I to O–I was hindered. With triflate counterion dissociating, it was likely that cationic hypervalent iodine reagents tended to attack the C2-atom of the enolate from the *Re*-face rather than the *Si*-face of β-ketoamides chelated with Ni/**L-PisEPh**, because the latter was strongly shielded by the aromatic ring and the *tert*-butyl of β-ketoamides. The intermediate (**TS1**) rapidly performed reductive elimination to give the desired *R*-configured product in accord with the X-ray analysis of **3aa**.[11]

Scheme 4. Proposed Stereochemical Model



In summary, we have developed an efficient chiral *N,N′*-dioxide/$Ni(OTf)_2$ complex catalytic system for the α-vinylation of β-keto amides/esters with hypervalent iodine salts under mild reaction conditions. The desired vinyl-substituted β-keto amides/esters derivatives were afforded in high yields and ee values (up to 99% yield and 99% ee). In particular, this is also the first example for enantioselective α-vinylation/alkynylation/arylation of β-keto amides/esters simultaneously catalyzed by a catalytic system. Further application of hypervalent iodine salts and chiral *N,N′*-dioxide–metal complexes in asymmetric synthesis is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02785.

Experimental details; analytical data (NMR, HPLC, and ESI-HRMS) (PDF)

X-ray crystallographic data for **3aa** (CIF)

X-ray crystallographic data for **4aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1424042 (**3aa**) and CCDC 1424041 (**4aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambrige Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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