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Synthetic Methods

Electrophilic Activation of α,β-Unsaturated Amides: Catalytic Asymmetric Vinylogous Conjugate Addition of Unsaturated γ-Butyrolactones

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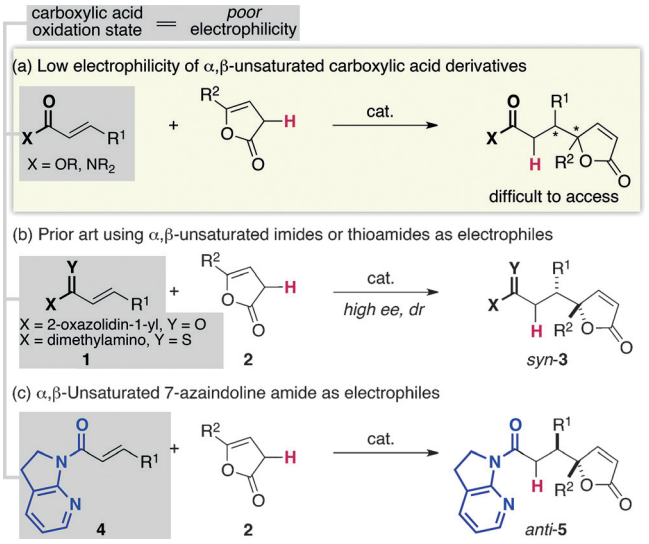
Abstract: Although catalytic asymmetric conjugate addition reactions have remarkably advanced over the last two decades, the application of less electrophilic α,β-unsaturated carboxylic acid derivatives in this useful reaction manifold remains challenging. Herein, we report that α,β-unsaturated 7-azaindoline amides act as reactive electrophiles to participate in catalytic diastereo- and enantioselective vinylogous conjugate addition of γ-butyrolactones in the presence of a cooperative catalyst comprising of a soft Lewis acid and a Brønsted base. Reactions mostly reached completion with as little as 1 mol% of catalyst loading to give the desired conjugate adducts in a highly stereoselective manner.

Conjugate addition reactions are advantageous for assembling nucleophiles and electron-deficient olefins into larger molecular architectures. In particular, C–C bond-forming conjugate addition reactions play a crucial role in constructing carbon skeletons of interest and also have a number of applications in modern organic syntheses.[1] In this context, considerable advances rendered the reaction catalytic and stereoselective to efficiently afford useful nonracemic building blocks. In general, the reaction efficiency largely relies on the electrophilic character of electron-deficient olefins (electrophiles), and relatively electrophilic substrates, for example, α,β-unsaturated ketones (enones), α,β-unsaturated aldehydes (enals), and nitroolefins, are widely utilized. In contrast, less electrophilic α,β-unsaturated carboxylic acid derivatives are not as well explored due to their poor electrophilicity, despite the synthetic utility of the prospective conjugate adducts. This is particularly true when the nucleophile is catalytically generated in situ, making it generally less reactive than organometallic reagents, which remains a major drawback to be addressed.

γ-Butenolides have attracted particular attention in the chemical community, because: 1) γ-butenolide units are present in a myriad of natural products;[2] and 2) they are nucleophilic at the γ-carbon upon deprotonative activation, which allows numerous vinylogous additions.[3,4] Catalytic asymmetric vinylogous conjugate addition reactions of γ-butenolides to electron-deficient olefins constitutes an important tool for producing chiral building blocks containing γ-butenolide units,[5–7] but few studies have provided examples using α,β-unsaturated carboxylic acid derivatives (Scheme 1 a). Zhang et al. disclosed



Scheme 1. Catalytic asymmetric conjugate addition of butenolides to α,β-unsaturated carboxylic acid derivatives.

that α,β-unsaturated imides serve as reactive electrophiles with thiourea/amine organocatalysts (Scheme 1 b).[8a] We reported that α,β-unsaturated thioamides exhibit sufficient electrophilicity in the presence of a soft Lewis acid catalyst to undergo smooth vinylogous addition of γ-butenolides, in which chemoselective activation of the soft Lewis basic thioamide functionality has a pivotal role in compensating for the low electrophilicity.[8b] Although both the reaction efficiency and stereoselectivity of the above-mentioned protocols are favorable, imides are doubly activated by two carbonyl groups and thioamides are uncommon functional groups associated with tedious preparation procedures. Herein, we report an alternative and more tractable α,β-unsaturated carboxylic acid derivatives, α,β-unsaturated 7-azaindoline amides, for catalytic asymmetric vinylogous conjugate addition of γ-butenolides (Scheme 1 c). The amides are easily prepared and are bench stable, and the

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observed diastereoselectivity compliments that observed in the reaction by using α,β-unsaturated imides and thioamides. The reactions mostly proceed with as little as 1 mol% of catalyst loading to give high yield and stereoselectivity.

In our search for alternative α,β-unsaturated carboxylic acid derivatives that can be catalytically activated, we reasoned that specific activation by a soft Lewis acid would be key to enhancing the electrophilicity at the β-carbon. Recently, we found that a 7-azaindoline amide functionality is a particularly effective structural motif for chemoselective and deprotonative activation.[9] Although the amide inherently prefers the *E*-conformation over the *Z*-conformation, the *Z*-conformation becomes dominant upon coordination to a soft Lewis acid to produce a chelated structure. This activated form facilitates catalytic deprotonation in the presence of a Brønsted base catalyst, rendering catalytic enolization of low-acidic amides by a soft Lewis acid/Brønsted base cooperative catalysis.[10] We anticipated that this activation mode would be valid for electrophilic activation; the combination of the α,β-unsaturated 7-azaindoline amide and a soft Lewis acid produces a similar chelated structure with a *Z*-amide conformation, exhibiting enhanced electrophilicity at the β-carbon to accept the nucleophilic addition of in situ generated active nucleophiles. To explore catalytic asymmetric conjugate addition to the α,β-unsaturated 7-azaindoline amides, conformational analysis was conducted with archetypal α,β-unsaturated amide **4a** bearing a β-Ph group (Figure 1). The *E*-conformation of **4a** was unequivocally confirmed in solid state by X-ray crystallography, and the conformation was retained in solution according to ^{1}H NMR analysis in [D$_8$]THF. Although characteristic olefinic protons appeared with the β-proton (H$_b$) more downfield than the α-proton (H$_a$) for typical α,β-unsaturated carbonyl compounds, the α-proton (H$_a$) appeared more downfield shifted than the β-proton (H$_b$) in this specific case, strongly suggesting that a hydrogen-bonding interaction of the α-proton (H$_a$) and a pyridyl nitrogen of the 7-azaindoline unit in *E*-conformation.[11] Upon the addition of a Cu^I/(*R*)-xyl-BINAP complex to **4a**, the α-proton (H$_a$) was significantly shifted upfield, which is ascribed to the breakdown of the above-mentioned hydrogen bonding and indicative of the chelated *Z*-conformation. The NOE signals observed between the α-proton (H$_a$) and aliphatic protons of the 7-azaindoline group are consistent with the *Z*-conformation. The *Z*-conformation was unequivocally determined by X-ray crystallography in the solid state.[12]

Given the premise of the activation of α,β-unsaturated 7-azaindoline amide **4a** with the Cu^I complex, conditions for enantioselective addition of angelica lactone **2a** to **4a** were screened in combination with Barton's base as a Brønsted base (Table 1). Chiral biaryl-type bisphosphines quickly emerged as

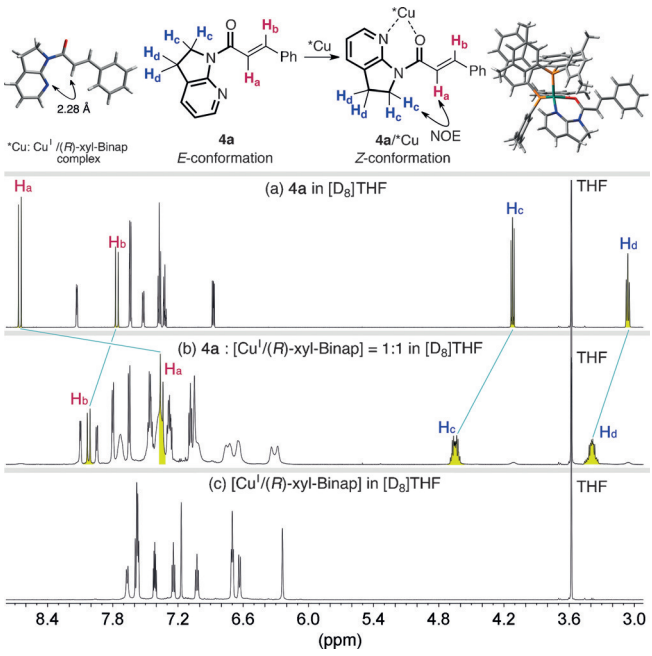
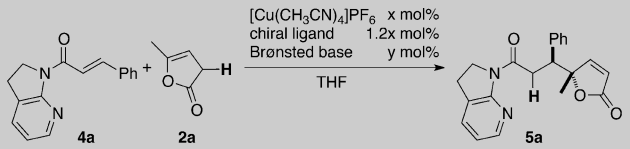
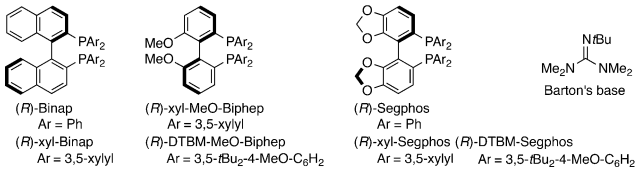


Figure 1. Conformational change of α,β-unsaturated 7-azaindoline amide **4a** was evidenced by ^{1}H NMR and X-ray crystallographic analysis. Color code for X-ray structure: hydrogen white, carbon gray, nitrogen blue, oxygen red, phosphorus orange, copper green.

Table 1. Catalytic asymmetric conjugate addition of angelica lactone **2a** to α,β-unsaturated 7-azaindoline amide **4a**[a]



Entry	Chiral ligand	*x*	Brønsted base	*y*	*T* [°C]	*t* [h]	Yield[b] [%]	*anti*/*syn*[b]	*ee*[c] [%]
1	(*R*)-Binap	5	Barton's base	5	0	3	>99	4/1	54
2	(*R*)-xyl-Binap	5	Barton's base	5	0	3	>99	13/1	92
3	(*R*)-Segphos	5	Barton's base	5	0	3	>99	3/1	58
4	(*R*)-xyl-Segphos	5	Barton's base	5	0	3	>99	13/1	85
5	(*R*)-DTBM-Segphos	5	Barton's base	5	0	3	23	>20/1	97
6	(*R*)-xyl-MeO-Biphep	5	Barton's base	5	0	3	>99	9/1	87
7	(*R*)-DTBM-MeO-Biphep	5	Barton's base	5	0	3	12	14/1	96
8	(*R*)-xyl-Binap	5	Barton's base	5	−40	3	>99	>20/1	96
9	(*R*)-xyl-Binap	5	DBU	5	−40	3	43	17/1	96
10	(*R*)-xyl-Binap	5	*i*Pr$_2$NEt	5	−40	3	0	–	–
11	(*R*)-xyl-Binap	5	Et$_3$N	5	−40	3	0	–	–
12[d]	(*R*)-xyl-Binap	1	Barton's base	5	−40	1	>99	>20/1	96
13	(*R*)-xyl-Binap	1	–	0	−40	24	0	–	–
14	–	0	Barton's base	5	−40	24	0	–	–



[a] **2a**: 0.3 mmol, **4a**: 0.1 mmol. [b] Determined by ^{1}H NMR analysis. [c] Values of *ee* of *anti* diastereomer; determined by chiral stationary-phase HPLC analysis. [d] **2a**: 0.15 mmol, **4a**: 0.1 mmol. Isolated yield.

suitable ligands in this catalytic system to give the desired conjugate adduct **5a** at 0 °C with reasonable stereoselectivity (Table 1, entries 1–7). Although we observed higher stereoselectivity by increasing the steric factor of the substituents on phosphorous, ligands with DTBM substituents significantly retarded the reaction (Table 1, entries 5, 7). A less bulky ligand, for example, (*R*)-xyl-Binap, at a lower temperature (−40 °C) exclusively gave *anti*-**5a** with high enantioselectivity (entry 8).[13] Barton's base was indispensable, and other common amine bases performed worse under otherwise identical conditions (Table 1, entries 9–11). Although these reactions were run for three hours to screen various conditions, the reaction seemed to proceed rapidly and reached completion within 1 h; the conditions could be further optimized to as little as 1 mol% of the Cu^{I} catalyst and 1.5 equivalents of **2a** (entry 12).[14] The cooperative work of Cu^{I} complex and Barton's base was crucial to activate both the electrophile (**4a**) and nucleophile (**2a**), and the reaction did not proceed at all in the absence of either (Table 1, entries 13, 14). The expeditious progress of the reaction was specific for 7-azaindoline amide. Other α,β-unsaturated carboxylic acid derivatives **6**–**10** gave no reaction under these catalytic conditions (Figure 2); indoline amide **6**, isomeric azaindoline amide **7**, and dimethylamide **9** were not able to form a bidentate coordination with Cu^{I} and the reactions failed. *N*-Methyl-(2-pyridyl)amide (**8**) was unreactive despite its bidentate coordination capability. Esters, including benzylidene malonate **11**, were not sufficiently electrophilic.

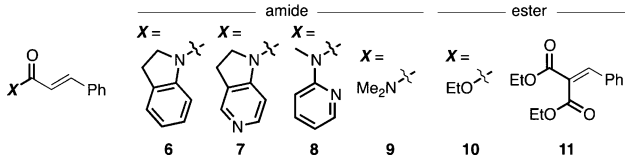
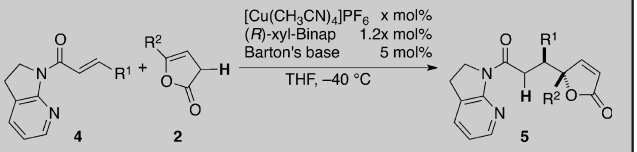


Figure 2. Structure of unsuccessful electrophiles.

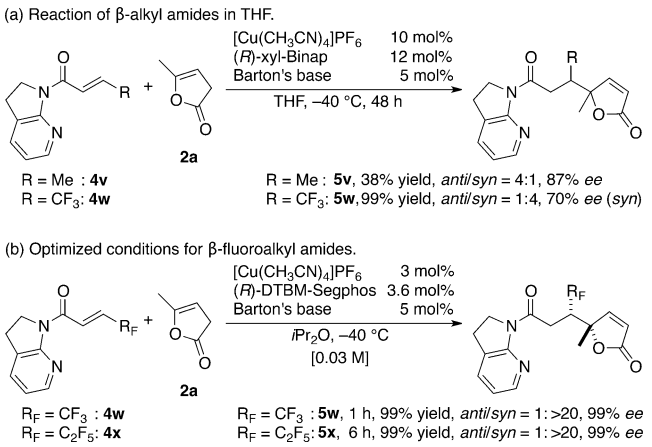
Substrate scope is delineated in Table 2, showing the production of conjugate adducts bearing consecutive tri- and tetrasubstituted stereogenic centers, mostly within one hour with 1 mol% of catalyst loading. Irrespective of the substitution pattern of the Me group on the β-aryl substituent, generally high reactivity and stereoselectivity were observed (entries 3–5). Various electron-withdrawing groups, for example, $-CF_3$, –F, –Cl, –Br, –OAc, and –CN, on the β-aryl substituent were tolerated (Table 2, entries 6–12). Electron-donating MeO or TBSO groups retarded the reaction, requiring 3 mol% of catalyst loading for completion, albeit with uniformly high stereoselectivity (entries 13–16). Soft Lewis basic heteroaromatics, which may potentially coordinate to Cu^{I} catalyst and suppress the catalysis, had little negative effect (Table 2, entries 18, 19). 1,4-Addition exclusively proceeded with amide-conjugated 1,3-dienes **4s** and **4t** and 1,3-enyne **4u** without forming 1,6-adducts (Table 2, entries 20–22). γ-Bn- and γ-allyl-substituted β,γ-unsaturated γ-butyrolactones **2b** and **2c** were also applicable to give the corresponding products **5ab** and **5ac** in high yield and stereoselectivity, although a longer reaction time was required (Table 2, entries 23, 24). Catalyst loading could be reduced to as little as 0.1 mol% and run on gram scale (entry 2). β-Alkyl amide **4v** exhibited poor reactivity and diastereoselectivity, whereas β-CF_3 amide **4w** unexpectedly gave the *syn*-diastereomer predominantly with high yield (Scheme 2a). A slight

Table 2. Substrate scope of γ-substituted β,γ-unsaturated γ-butyrolactones **2** to α,β-unsaturated 7-azaindoline amides **4**.[a]

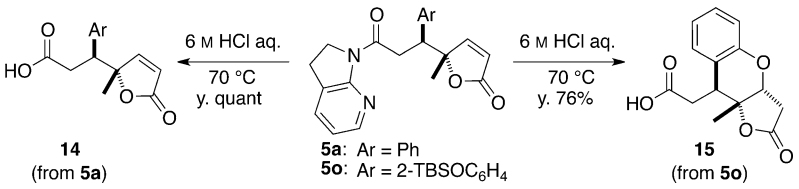


Entry	**4** R^1	**2** R^2	*x*	pdt	*t* [h]	Yield[b] [%]	*anti* /*syn*[c]	*ee*[d] [%]
1	Ph **4a**	Me **2a**	1	**5a**	1	>99	>20/1	96
2[e]	Ph **4a**	Me **2a**	0.1	**5a**	48	91	>20/1	96
3	2-MeC_6H_4 **4b**	Me **2a**	1	**5b**	1	97	>20/1	97
4	3-MeC_6H_4 **4c**	Me **2a**	1	**5c**	1	>99	>20/1	96
5	4-MeC_6H_4 **4d**	Me **2a**	1	**5d**	1	>99	16/1	97
6	4-$CF_3C_6H_4$ **4e**	Me **2a**	1	**5e**	1	>99	>20/1	93
7	4-FC_6H_4 **4f**	Me **2a**	1	**5f**	1	>99	>20/1	96
8	4-ClC_6H_4 **4g**	Me **2a**	1	**5g**	1	>99	>20/1	95
9	2-BrC_6H_4 **4h**	Me **2a**	1	**5h**	1	>99	>20/1	98
10	4-BrC_6H_4 **4i**	Me **2a**	1	**5i**	1	>99	>20/1	95
11	4-$AcOC_6H_4$ **4j**	Me **2a**	1	**5j**	1	95	20/1	95
12	4-NCC_6H_4 **4k**	Me **2a**	1	**5k**	1	98	>20/1	91
13[f]	2-$MeOC_6H_4$ **4l**	Me **2a**	3	**5l**	3	99	>20/1	97
14[f]	3-$MeOC_6H_4$ **4m**	Me **2a**	3	**5m**	3	99	>20/1	93
15[f]	4-$MeOC_6H_4$ **4n**	Me **2a**	3	**5n**	3	>99	>20/1	97
16	2-$TBSOC_6H_4$ **4o**	Me **2a**	3	**5o**	2	91	13/1	91
17	4-$TBSOC_6H_4$ **4p**	Me **2a**	1	**5p**	1	>99	>20/1	97
18	3-pyridyl **4q**	Me **2a**	1	**5q**	1	98	>20/1	95
19	2-thienyl **4r**	Me **2a**	1	**5r**	1	93	>20/1	96
20	(*E*)-cinnamyl **4s**	Me **2a**	1	**5s**	1	>99	>20/1	96
21	(*E*)-$CH_3CH{=}CH$ **4t**	Me **2a**	1	**5t**	1	88	>20/1	97
22	$PhC{\equiv}C$ **4u**	Me **2a**	1	**5u**	1	99	>20/1	92
23	Ph **4a**	Bn **2b**	1	**5ab**	12	98	>20/1	93
24	Ph **4a**	allyl **2c**	1	**5ac**	12	99	>20/1	92

[a] **2**: 0.15 mmol, **4**: 0.1 mmol. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Value of *ee* of *anti* diastereomer; determined by chiral stationary-phase HPLC analysis. [e] Run on 1.25 g of **4a**; 6 mol% of Barton's base was used. [f] 3 equiv of **2a** (0.3 mmol) was used.



Scheme 2. Reactions of β-alkyl and β-fluoroalkyl amides.

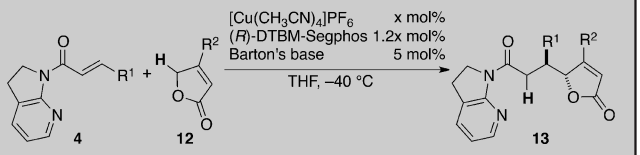


Scheme 3. Transformation of the products.

modification of the conditions, (*R*)-DTBM-Segphos as the ligand and *i*Pr$_2$O as the solvent, enhanced the *syn*-preference, as well as enantioselectivity, which was also valid for β-C_2F_5 amide **4x** (Scheme 2b).[15] Retro-reaction and epimerization were barely detected, suggesting that β-fluoroalkyl substrates **4w** and **4x** kinetically favored the formation of the *syn*-diastereomer.

α,β-Unsaturated γ-butyrolactones **12** were also applicable in the present catalytic system to give **13** bearing consecutive trisubstituted stereogenic centers (Table 3). The reaction was promoted by only 1 mol% of Cu^{I} catalyst and more sterically demanding (*R*)-DTBM-Segphos was optimal for less bulkier nucleophile **12a**, except for the reactions of unsaturated amide **4b** and **i** bearing an *o*-Me or *o*-Br group, with which less bulky (*R*)-xyl-Binap performed better (Table 3, entries 2, 8). Amide **4n** with an electron-donating *p*-MeO group required 3 mol% of the catalyst (entry 10), and β-Me substituted nucleophile **12b** also preferred (*R*)-xyl-Binap (Table 3, entry 12) as a chiral ligand.

Table 3. Substrate scope of β-substituted α,β-unsaturated γ-butyrolactones **12** to α,β-unsaturated 7-azaindoline amides **4**.[a]



Entry	**4** R^1	**12** R^2	*x*	pdt	*t* [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	Ph **4a**	H **12a**	1	**13a**	3	98	>20/1	95
2[e]	2-MeC_6H_4 **4b**	H **12a**	1	**13b**	3	94	>20/1	93
3	3-MeC_6H_4 **4c**	H **12a**	1	**13c**	24	95	>20/1	97
4	4-MeC_6H_4 **4d**	H **12a**	1	**13d**	24	95	>20/1	96
5	4-$CF_3C_6H_4$ **4e**	H **12a**	1	**13e**	24	92	>20/1	92
6	4-FC_6H_4 **4f**	H **12a**	1	**13f**	24	97	>20/1	96
7	4-ClC_6H_4 **4g**	H **12a**	1	**13g**	24	99	>20/1	97
8[e]	2-BrC_6H_4 **4h**	H **12a**	1	**13h**	24	99	>20/1	90
9	4-BrC_6H_4 **4i**	H **12a**	1	**13i**	24	92	>20/1	95
10	4-MeOC_6H_4 **4n**	H **12a**	3	**13n**	24	95	>20/1	98
11	2-thienyl **4r**	H **12a**	1	**13r**	24	91	>20/1	98
12[e]	Ph **4a**	Me **12b**	1	**13ab**	3	93	>20/1	97

[a] **12**: 0.3 mmol, **4**: 0.1 mmol. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Value of *ee* of *anti* diastereomer; determined by chiral stationary-phase HPLC analysis. [e] (*R*)-xyl-Binap was used as a chiral ligand.

The 7-azaindoline moiety of product **5a** could be readily hydrolyzed to give **14** under acidic conditions with the butyrolactone ring intact (Scheme 3). Treatment of **5o** bearing a phenolic *tert*-butyldimethylsilyl (TBS) ether with identical conditions gave bicyclic compound **15** via hydrolysis/desilylation and subsequent phenol-selective cyclization.

In conclusion, α,β-unsaturated 7-azaindoline amides, which are in the carboxylic acid oxidation state, served as reactive conjugate addition acceptors when using butyrolactones as nucleophiles in a cooperative catalytic system. Reactions mostly completed with 1 mol% of the catalyst with high stereoselectivity, and the observed *anti*-selectivity was complementary to the prior art by using imides and unsaturated thioamides as electrophiles. The amide moiety was chemoselectively hydrolyzed for further manipulations.

Acknowledgements

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Keywords: asymmetric catalysis · azaindoline · butenolide · conjugate addition · cooperative catalysis

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[11] Confirmed by ^{1}H–^{13}C HMBC analysis; see the Supporting Information.

[12] Single crystal was obtained from the $[Cu(CH_3CN)_4]PF_6$/*rac*-xyl-Binap/**4a** mixture.

[13] Absolute configuration was determined by X-ray crystallographic analysis; see the Supporting Information for details.

[14] Reducing the amount of Barton's base to 1 mol% led to a significant decrease in the yield.

[15] Products **5v** and **w** were highly insoluble in iPr_2O, and the clear reaction mixture became a white suspension, even at 0.03 M, when the reaction proceeded.

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