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Asymmetric Allylic Alkylation with Deconjugated Carbonyl Compounds: Direct Vinylogous Umpolung Strategy

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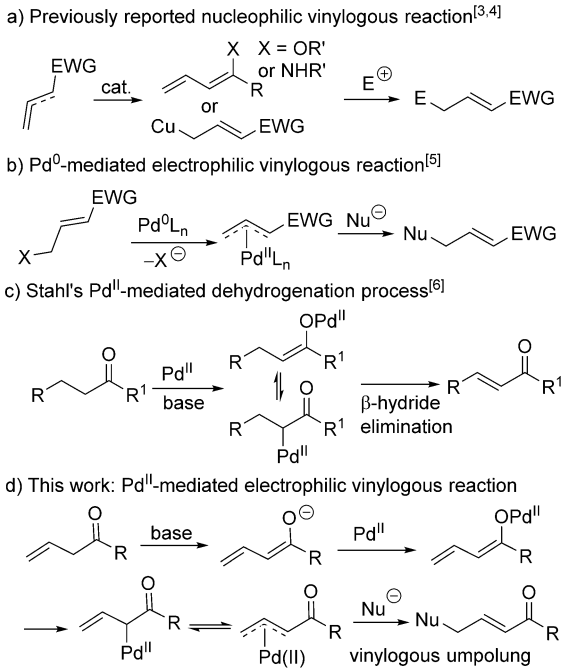
Abstract: *An atom-economic and highly efficient vinylogous umpolung strategy is developed for deconjugated carbonyl compounds, which generate electron-deficient π-allylpalladium complexes with $Pd(OAc)_2$ under ligand-free conditions. In cooperation with a chiral-phosphonium-based phase-transfer catalyst, the asymmetric direct oxidative allylic alkylations of 3-substituted oxindoles are furnished under O_2 atmosphere. The γ- or even remote ε-regioselective alkylation products, with substantial substituents, are delivered with excellent enantioselectivity, and can be further used to access diverse chiral spirocyclic architectures effectively. The Mukaiyama dienol silyl ether can be utilized similarly, indicating that the current active π-allylpalladium species results from tautomerization of the Pd^{II}-dienolate intermediate.*

The nucleophilic vinylogous reaction of unsaturated systems, including its asymmetric version, provides a straightforward and powerful protocol to access γ-functionalized α,β-unsaturated carbonyl compounds.[1] Apart from the early exploration by using dienol silyl ether precursors,[2] recently, direct asymmetric vinylogous reactions by in situ generation of either dienoate or dienamine intermediates have attracted much attention.[3] Shibasaki also developed a direct vinylogous strategy via a γ-copper species (Scheme 1 a).[4] In contrst, α,β-unsaturated systems bearing a γ-leaving group can deliver electron-deficient π-allylpalladium complexes in the presence of a Pd^0 source, thus rendering alternative electrophilic vinylogous-type alkylation reactions (Scheme 1 b).[5] Nevertheless, there is still no report involving direct electrophilic alkylation reactions with simple unsaturated carbonyls by a vinylogous umpolung strategy.

In 2011, Stahl developed Pd^{II}-catalyzed direct dehydrogenation of ketones to the corresponding α,β-enones in the presence of oxygen, by forming Pd^{II}-enolate species and subsequent β-hydride elimination (Scheme 1 c).[6] Inspired by the above-mentioned studies, we envisaged that the readily generated dienolates from allyl carbonyls would coordinate with Pd^{II} salts, and produce the electron-deficient π-allylpalladium complexes by tautomerization, as proposed in Scheme 1 d. As a result, allylic alkylations of suitable nucleophiles would be accomplished in a direct vinylogous umpolung manner.



Scheme 1. Diverse activation modes for unsaturated systems. EWG = electron-withdrawing group.

The initial reaction of the 3-phenyloxindole **1a** and allyl phenyl ketone **2a** was investigated under the catalysis of $Pd(OAc)_2$ (10 mol%), in the presence of KOAc (0.5 equiv) and O_2 (1 atm), at room temperature, but no reaction occurred (Table 1, entry 1). Gratifyingly, good conversion was observed by adding the phase-transfer catalyst (PTC) tetrabutylammonium bromide (TBAB, 20 mol%), and the γ-regioselective oxidative cross-coupling product **3a** was isolated in a good yield after 8 hours (entry 2). It should be noted that very poor reaction was observed under Ar. In addition, only the Michael adduct **3a′** was obtained in a low yield by using the conjugated enone **2a′** (entry 3), indicating that the inducing effect of the previously positioned β,γ-C=C bond would be crucial for generating the required dienolate intermediate (Scheme 1 d).[7] Encouraged by these results, we explored the potential asymmetric version by the cooperative catalysis of $Pd(OAc)_2$ and chiral PTC.[8] While poor yield and enantioselectivity were obtained with ammonium salt **C1** (Table 1, entry 4), it was found that better reaction

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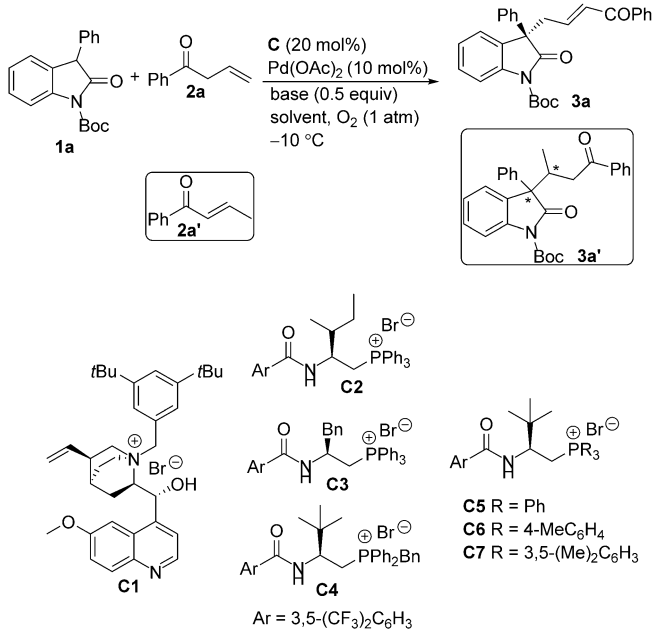
Table 1: Screening conditions of asymmetric vinylogous umpolung reaction of the oxindole **1a** and allyl ketone **2a**.[a]



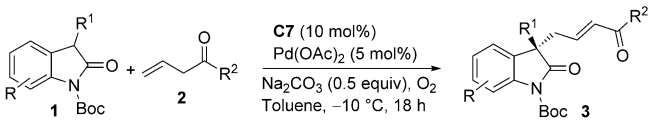
Entry	C	Base	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	–	KOAc	Toluene	8	–	–
2[d]	TBAB	KOAc	Toluene	8	79	–
3[d,e]	TBAB	KOAc	Toluene	8	16[e]	–
4[d]	**C1**	KOAc	Toluene	8	35	27
5[d]	**C2**	KOAc	Toluene	8	48	34
6[d]	**C3**	KOAc	Toluene	8	37	20
7[d]	**C4**	KOAc	Toluene	8	56	64
8	**C4**	KOAc	Toluene	15	58	80
9	**C5**	KOAc	Toluene	15	89	81
10	**C6**	KOAc	Toluene	15	87	88
11	**C7**	KOAc	Toluene	15	91	97
12	**C7**	KOAc	DCM	15	30	81
13	**C7**	KOAc	*o*-Xylene	15	71	97
14	**C7**	KOAc	$PhCF_3$	15	33	92
15[f]	**C7**	KOAc	Toluene	18	81	97
16[f]	**C7**	K_2CO_3	Toluene	18	44	88
17[f]	**C7**	Na_2CO_3	Toluene	18	91	97
18[f]	**C7**	K_3PO_4	Toluene	18	82	98
19[g]	**C7**	Na_2CO_3	Toluene	36	68	98
20[f,h]	**C7**	Na_2CO_3	Toluene	24	63	97

[a] Unless noted otherwise, reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), **C** (20 mol%), $Pd(OAc)_2$ (10 mol%), base (0.5 mmol) in solvent (1.0 mL) under O_2 (1 atm). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At RT. [e] **2a′** was used and **3a′** was obtained in 16% yield (>19:1 d.r.). [f] With **C7** (10 mol%), $Pd(OAc)_2$ (5 mol%). [g] With **C7** (5 mol%), $Pd(OAc)_2$ (2.5 mol%). [h] Under air. Boc = *tert*-butoxycarbonyl, DCM = dichloromethane.

could be attained by employing the L-amino-acid-derived phosphonium salts **C2**–**C4** (entries 5–7),[9] and a good *ee* value was gained with **C4** at −10 °C (entry 8). We further modified the phosphonium moiety of **C4**-based PTCs (entries 9–11), and excellent yield and enantioselectivity were achieved with **C7**, bearing a 3,5-dimethylphenyl group (entry 11). Inferior data were obtained in other solvents (entries 12–14). Since reducing the catalyst loadings resulted in a lower yield (entry 15), a few inorganic bases were screened (entries 16–18), and Na_2CO_3 turned out to be the optimal one (entry 17). In addition, the yield was significantly diminished by further reducing the catalyst loadings but with retained excellent enantiocontrol (entry 19), and similar inferior results were observed when open to air (entry 20).[10]

With the optimized reaction conditions in hand, we examined the scope and limitations of this new vinylogous umpolung reaction, under the cooperative catalysis of $Pd(OAc)_2$ (5 mol%) and PTC **C7** (10 mol%). The results are summarized in Table 2. For the reactions with **2a**, uniformly high to excellent enantioselectivities were obtained by introducing diverse substituents into the oxindole core of the nucleophiles **1** (entries 2–6), whereas slightly lower yields were observed for those with electron-withdrawing groups (entries 4–6). Outstanding enantiocontrol was attained for other 3-aryl-substituted oxindoles (entries 7–9). Notably, an oxindole bearing a 1-pyrrolyl group could be successfully applied (entry 10), and outstanding *ee* values were generally afforded by introducing various benzyl (entries 11–13) or

Table 2: Substrate scope and limitations of asymmetric vinylogous umpolung reactions.[a]

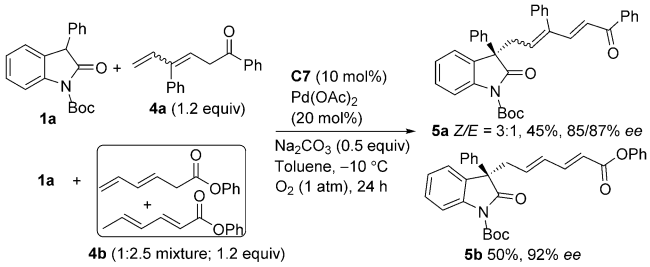


Entry	R, R^1	R^2	Yield [%][b]	*ee* [%][c]
1	H, Ph	Ph	**3a**, 91	97
2	5-Me, Ph	Ph	**3b**, 85	98
3	6-MeO, Ph	Ph	**3c**, 83	96
4	5-F, Ph	Ph	**3d**, 73	98
5[d]	6-Cl, Ph	Ph	**3e**, 56	98
6	7-Cl, Ph	Ph	**3f**, 69	86
7	H, 3,5-$Me_2C_6H_3$	Ph	**3g**, 91	92
8	H, 4-$MeOC_6H_4$	Ph	**3h**, 89	98
9	H, 4-FC_6H_4	Ph	**3i**, 78	98
10	H, 1-Pyrrolyl	Ph	**3j**, 68	97
11	H, Bn	Ph	**3k**, 83	97
12	H, 3,4-$(MeO)_2Bn$	Ph	**3l**, 57	95
13	H, 3-FurylCH_2-	Ph	**3m**, 53	96
14	H, -$C_2H_4NHCO_2Me$	Ph	**3n**, 86	86[e]
15	H, -CH_2COCH_3	Ph	**3o**, 50	97
16	H, -CH_2CO_2Et	Ph	**3p**, 64	95
17	H, Ph	3-MeC_6H_4	**3q**, 88	97
18	H, Ph	3-$MeOC_6H_4$	**3r**, 87	98
19	H, Ph	4-FC_6H_4	**3s**, 68	97
20	H, Ph	2-ClC_6H_4	**3t**, 72	95
21	H, Ph	*N*-Ts-3-indolyl	**3u**, 93	95
22	H, Ph	3-Furyl	**3v**, 80	98
23	H, Ph	PhC_2H_4-	**3w**, 49	96
24	H, Ph	OPh	**3x**, 64	98
25[f]	5-Me, Ph	Ph	**3b**, 76	97

[a] Unless noted otherwise, reactions were performed with **1** (0.1 mmol), **2** (0.12 mmol), **C7** (10 mol%), $Pd(OAc)_2$ (5 mol%) and Na_2CO_3 (0.5 mmol) in toluene (1.0 mL) under O_2 (1 atm), at −10 °C for 18 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At −20 °C. [e] The absolute configuration of chiral **3n** was determined by X-ray analysis of its derivative **12′** (see the Supporting Information).[11] The other products were assigned by analogy. [f] At a 1.0 mmol scale.

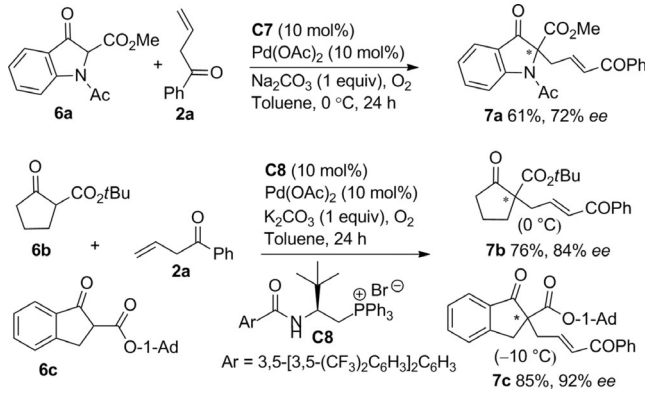
even functionalized alkyl groups (entries 14–16). In contrast, we turned our attention to the reactions of **1a** with a variety of allyl ketones (**2**). In general, an array of allyl aryl or heteroaryl ketones (**2**) were well tolerated (entries 17–22), whereas an allyl alkyl ketone gave a fair yield (entry 23). Pleasingly, a phenyl but-3-enoate also showed good reactivity under the same reaction conditions, and a modest yield with excellent enantioselectivity was gained accordingly (entry 24). We also tested the asymmetric reaction at a larger scale, and comparably good results were delivered (entry 25).

Moreover, the deconjugated 3,5-dienone[7b] **4a** and 3,5-dienoate **4b** (a mixture containing the conjugated one) were utilized in the umpolung reaction with **1a** through the cooperative catalysis (Scheme 2). A more challenging remote ε-selective functionalization reaction was similarly accomplished. Higher loadings of $Pd(OAc)_2$ were necessary for better conversions, and the corresponding products, **5a** and **5b**, were obtained with high enantioselectivities, albeit in fair yields.



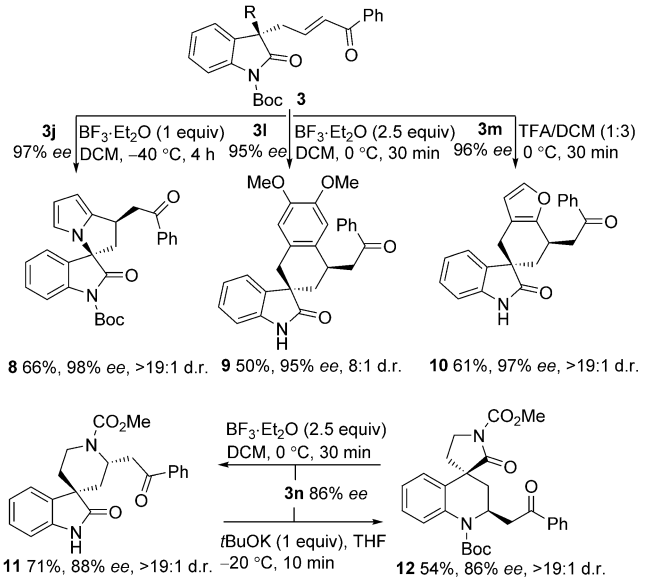
Scheme 2. Remote ε-functionalization with 3,5-diene carbonyl compounds.

In addition, other types of nucleophiles were further explored. As illustrated in Scheme 3, the 3-indolinone-2-carboxylate **6a** reacted with **2a** under similar catalytic conditions, giving the product **7a** in moderate yield and enantioselectivity. Furthermore, both the β-ketoesters **6b** and **6c** exhibited good reactivities with **2a**, and a bulkier phosphonium salt, **C8**, was developed to guarantee better enantiocontrol for the corresponding products **7b** and **7c**.



Scheme 3. More examples with other nucleophiles.

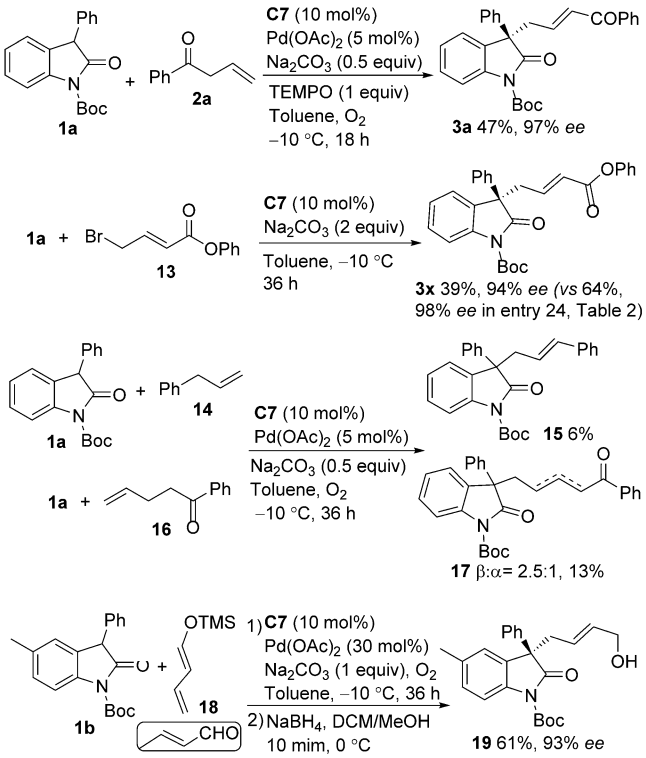
As illustrated in Scheme 4, the α,β-unsaturated ketone motif of the compounds **3** enables further transformations to produce diverse frameworks with higher molecular complexity. The cross-coupling products bearing electron-donating



Scheme 4. Synthetic transformations of the products.

aromatic rings furnished the spirooxindoles **8**–**10**, incorporating a 2,3-dihydro-1*H*-pyrrolizine, tetrahydronaphthalene, or tetrahydrobenzofuran ring system, respectively, by a highly diastereoselective intramolecular Friedel–Crafts reaction promoted by either $BF_3{\cdot}Et_2O$ or trifluoroacetic acid (TFA). A spirocyclic oxindole **11** bearing a piperidine unit was produced smoothly from the product **3n** through $BF_3{\cdot}Et_2O$-mediated aza-Michael addition. Interestingly, the spiro-pyrrolidine-quinoline skeleton **12** (the N-Boc deprotected derivative **12′** was confirmed by X-ray analysis)[11] was constructed in a modest yield with retained enantioselectivity by transamidation/aza-Michael addition using *t*BuOK.[12]

To elucidate the catalytic mechanism, more reactions were conducted. As outlined in Scheme 5, adding 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the catalytic reaction of **1a** and **2a** did not prohibit the conversion, indicating that a radical process would not be involved. In addition, phenyl 4-bromocrotonate **13** was used for the alkylation reaction with **1a** under the catalysis of **C7** without $Pd(OAc)_2$, and similar enantioselectivity for the product **3x** was obtained, albeit in a lower yield, suggesting that the Pd catalyst had limited impact on the stereochemistry. In contrast, the reaction of **1a** with allylbenzene **14** and γ,δ-enone **16** under the standard reaction conditions was tested, and only very low yield of the corresponding alkylation products **15** and **17**, respectively, was isolated. Moreover, although crotonaldehyde failed to react with **1b**, similar vinylogous umpolung allylic alkylation occurred by using its O-TMS dienol ether **18**, giving the product **19** in a modest yield with excellent enantioselectivity after reduction with $NaBH_4$, though with higher loadings of $Pd(OAc)_2$.[6d,e] These



Scheme 5. More experiments for elucidating the catalytic mechanism. TMS = trimethylsilyl.

results show that the current protocol with the deconjugated enone **2a** would preferably proceed via a Pd^{II}-dienolate species as proposed in Scheme 1 d, rather than by a Pd^{II}-mediated allylic C–H activation.[13,10]

In conclusion, we have developed an unprecedented direct vinylogous umpolung protocol for deconjugated β,γ-unsaturated carbonyl compounds with simple $Pd(OAc)_2$ under O_2 atmosphere and ligand-free conditions, by forming electron-deficient π-allylpalladium complexes via Pd^{II}-dienolate intermediates. Highly efficient γ-regioselective asymmetric allylic alkylations with 3-substituted oxindoles were furnished under the cooperative catalysis of a chiral phosphonium phase-transfer substance, generally giving the multifunctional products bearing an all-carbon-based quaternary stereocenter with excellent enantioselectivity. Moreover, this strategy could be expanded to remote ε-functionalizations with 3,5-diene-type carbonyls. An array of diversely structured spirocyclic frameworks could be further constructed from the oxidative cross-coupling products effectively. We believe that this atom-economic umpolung strategy of deconjugated carbonyl compounds will find more applications in organic synthesis. More results will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: conjugation · heterocycles · palladium · phase transfer catalysis · umpolung

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