Asymmetric Synthesis

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Asymmetric Allylic Alkylation of Cyclic Vinylogous Esters and Thioesters by Pd-Catalyzed Decarboxylation of Enol Carbonate and β-Ketoester Substrates**

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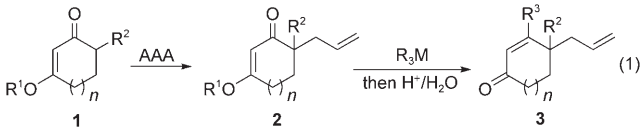
β-Alkoxy α,β-unsaturated ketones are versatile synthons for organic synthesis, as they serve as masked 1,3-dicarbonyl compounds in which the two ketone groups and adjacent carbon atoms may be selectively functionalized. Polysubstituted cyclic vinylogous esters are particularly useful for the synthesis of terpene, alkaloid, and steroidal natural products;[1] a practical method for their synthesis in enantioenriched form is therefore eminently desirable. The catalytic enantiomeric protocol to synthesize enones, such as **3**, was reported recently by Fuchs and co-workers, but was limited to monosubstituted enones ($R^2 = H$), and the relatively harsh conditions may further limit the access to highly functionalized enones.[2] Our strategy aimed to take advantage of an asymmetric allylic alkylation (AAA)/Stork–Danheiser addition sequence to furnish γ,γ-disubstituted cycloalkenones **3** [Eq. (1)].[3]



We initially attempted to access **2** with our previously reported method by alkylating the kinetically generated enolate of **1** with a combination of Pd^0, methyl allyl carbonate, and a chiral bidentate phosphine ligand.[4] The use of lithium diisopropyl amide (LDA) as the base (Li is essential for regiospecific enolate formation and alkylation) allowed quantitative formation of allylated products. However, we could not improve enantioselectivity beyond 30%. We there-

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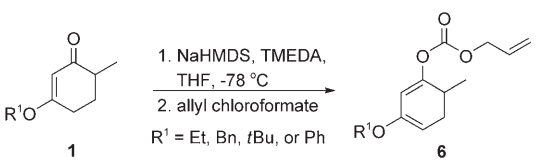
fore set about investigating an asymmetric variant of the Tsuji protocol for allylation, pioneered by Muzart and co-workers[5] and developed recently by us and others.[6] This strategy requires the preliminary synthesis of either allyl β-ketoesters or allyl enol carbonates of ketone **1**. Whereas efforts to synthesize the desired enol carbonates **4** gave only by-product **6** [Eq. (2); HMDS = hexamethyldisilazane, TMEDA = *N*,*N*,*N*',*N*'-tetramethyl-1,2-ethanediamine] or a low yield of **4** [Eq. (3); R^1 = Bn], the related β-ketoesters were available in excellent yields [Eq. (4)]. We then submitted these substrates to our decarboxylative alkylation conditions and were delighted to see product formation with excellent enantiomeric excess. Enol carbonate **4** was completely converted into the product. However, the conversion of the β-ketoesters was much worse, reflecting the additional energy



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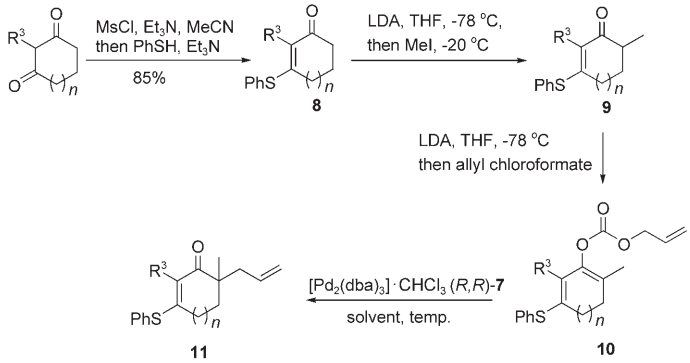
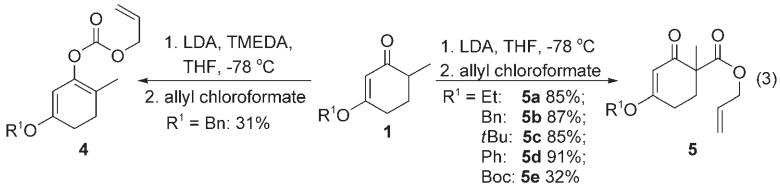


Scheme 1. The preparation of allyl carbonate **10** and the Pd-catalyzed asymmetric Tsuji reaction.



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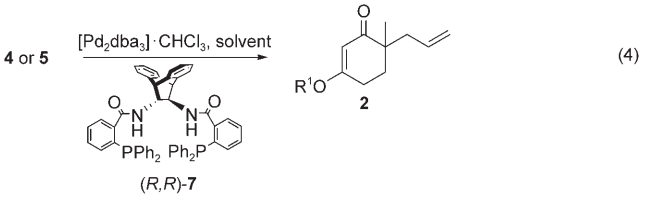


(4)

required to break a C–C bond in the decarboxylation step. This effect is exacerbated by the π-donating ability of the ether oxygen atom (Table 1, entries 2 and 4). Heating the reaction or addition of oxophilic Lewis acids failed to improve the conversion.[7] *O*-*tert*-Butyloxycarbonyl (Boc) and *O*-phenyl derivatives (Table 1, entries 5 and 6), in which the electron-donating power of the oxygen atom is attenuated,

Table 1: The optimized results for the reaction of **4** or **5**.[a]

Entry	Substrate	Solvent	Yield [%][b]	*ee* [%][c]
1	**4**	toluene	87	85
2	**5a**	1,4-dioxane	26	94
3	**5b**	THF	51	91
4	**5c**	1,4-dioxane	29	97
5	**5d**	1,4-dioxane	70	96
6	**5e**	THF	66	94

[a] All reactions were performed on a 0.1-mmol scale at 0.1 M at 23 °C overnight with 2.5 mol% of $[Pd_2dba_3]\cdot CHCl_3$ and 6 mol% of ligand. [b] Yield of the isolated products. [c] The *ee* values were determined by chiral HPLC on Chiralcel columns.

gave better conversions, although the synthesis of these substrates was achieved in much lower yield.

We reasoned that the poorer orbital overlap between sulfur and carbon would make the β-ketoesters or enol carbonates of vinylogous thioethers more reactive substrates. The generation of **9** proceeded as expected (Scheme 1).[8]

Surprisingly, the attempted formation of the β-ketoesters under the previously optimized conditions [Eq. (3)] predominantly afforded the allyl enol carbonates **10** instead. These proved to be excellent substrates for the allylation reaction (Table 2). Dioxane or THF at lower temperature were superior to other solvents for this reaction, an observation consistent with tight ion pairs as intermediates. Allylated products **11** containing five-, six-, and seven-membered rings are produced in excellent yield and enantioselectivity. Substitution at the 2-position is tolerated as well (Table 2, entries 2–4): the vinyl bromide is particularly useful for further functionalization. Remarkably, disubstitution at the 5-position is also tolerated (Table 2, entry 5), thus allowing the formation of adjacent quaternary centers in good enantiomeric excess.

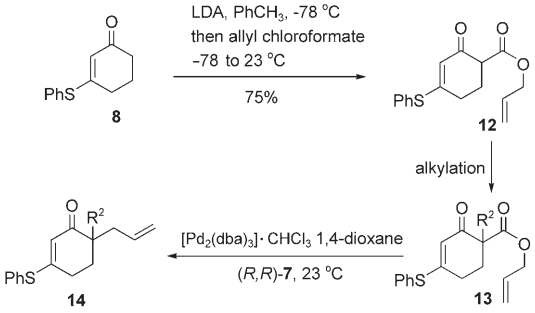
The related β-ketoesters were also available through a slightly modified route. Accordingly, the enolization of **8** with two equivalents of LDA in toluene at −78 °C followed by the addition of allyl chloroformate yielded β-ketoester **12** as the major product in 75% yield of the isolated product. Alkyla-

Table 2: The reaction of various allyl enol carbonates.[a]

Entry	*n*	R^3	R^4	Solvent	*T* [°C][b]	Yield [%][c]	*ee* [%][d]
1	1	H	H	THF	−20	100	98
2	1	CH_3	H	THF	0–4	100	99
3	1	Br	H	dioxane	23	97	86
4	1	Ph	H	dioxane	23	100	97
5	1	H	Me_2	THF	0–4	91	79
6	2	H	H	THF	0–4	100	94
7	0	Me	H	THF	0–4	96	80

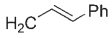
[a] All reactions were performed on a 0.1-mmol scale at 0.1 M overnight with 2.5 mol% of $[Pd_2dba_3]\cdot CHCl_3$ and 6 mol% of ligand. [b] Optimized temperature for the best *ee* value and conversion. [c] Yield of the isolated products. [d] The *ee* values were determined by chiral HPLC on Chiralcel columns.

tion by either S_N2 substitution or conjugate addition gave **13** in excellent yields (Scheme 2). These compounds were also excellent substrates for the decarboxylative alkylation reaction and products were formed in excellent yields and with generally excellent enantioselectivities (Table 3). The reaction tolerates a wide range of functionalities at R^2. We believe the reaction to proceed through an inner-sphere mechanism, in which the final bond-forming event occurs by reductive elimination of a Pd-bound enolate and π-allyl moiety.[6c,f] The successful reaction given in entry 15 lends further credence to this theory: the free enolate would undoubtedly deprotonate the tethered malonate, which could then be alkylated. We suggest that coordination of the side-chain functionality (Table 3, entry 5: C≡C; entries 8, 11, and 15: C=O) disrupts the transition state of the enantiorecognition step, thus resulting in the lower observed *ee* values (Scheme 3). Shorter (Table 3, entries 9 and 10) or longer (Table 3, entry 12) tethers to the coordinating group or increased steric congestion (Table 3, entry 6) disfavor this interaction and the *ee* values of the products return to ≥90%.

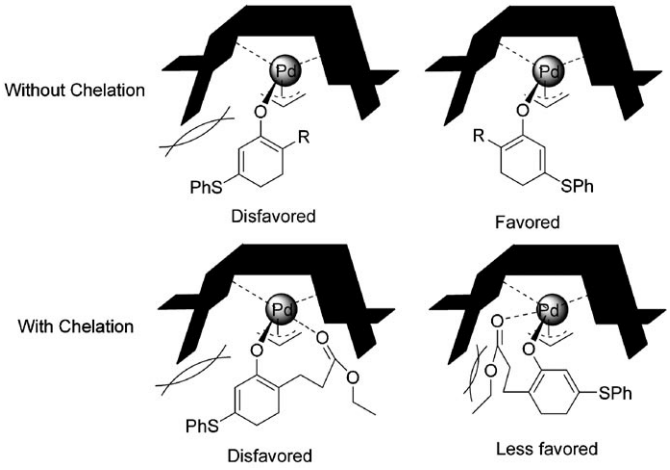


Scheme 2. The preparation of vinylogous thioester **13** and the Pd-catalyzed asymmetric Tsuji reaction.

Table 3: The reaction of various β-ketoesters **13** and **14**.[a]

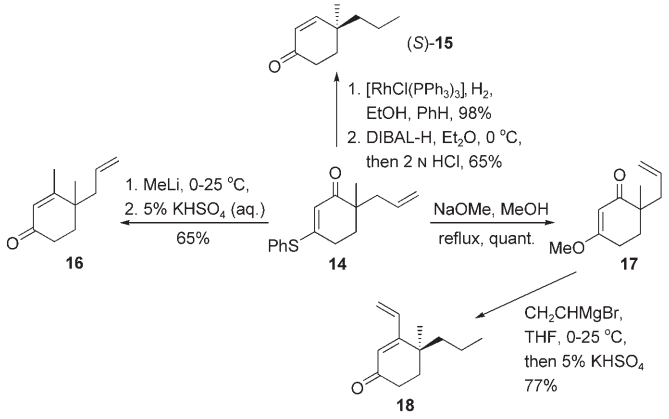
Entry	R^2	*T* [h]	Yield [%][b]	*ee* [%][c]
1	CH_3	16	75	100
2	CH_2Ph	16	78	92
3		2	98	95
4		16	84	91
5		4	83	72
6		1	89	91
7	CH_2CH_2CN	0.5	98	83
8	$CH_2CH_2C(O)CH_3$	6	75	57
9	$CH_2C(O)CH_3$	2	97	85
10	CH_2CO_2Et	1	80	92
11	$CH_2CH_2CO_2Et$	4	90	73
12	$CH_2(CH_2)_2CO_2Et$	2	86	94
13		0.5	87	95
14	$CH_2(CH_2)_2OBn$	16	65	93
15	$CH_2CH(CO_2tBu)_2$	2	97	36

[a] All reactions were performed on a 0.2-mmol scale at 0.1 M in 1,4-dioxane at 23 °C with 2.5 mol% of $[Pd_2dba_3]\cdot CHCl_3$ and 5.5 mol% of ligand. [b] Yield of the isolated products. [c] The *ee* values were determined by chiral HPLC on Chiralcel columns. TMS = trimethylsilyl.

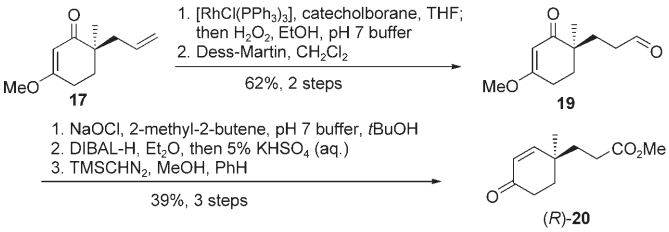


Scheme 3. Schematic representation of the mechanism of the enantiorecognition step with or without chelation.

The synthetic utility of the alkylated products was briefly investigated (Schemes 4 and 5). The addition of alkyllithium reagents[9] or diisobutylaluminium hydride (DIBAL-H) occurs selectively in a 1,2-fashion to afford γ,γ-disubstituted cyclohexenones on aqueous acidic work up. Conversion into the corresponding vinylogous methyl ester occurs readily on treatment with sodium methoxide in refluxing methanol,[10] to which Grignard reagents may be added directly. Along these lines, **14** was manipulated to afford known compounds **15** and **20**.[11] Comparison of optical rotation allowed us to assign the absolute stereochemistry of **14** as *R*, which is consistent with our previous results.[6c]



Scheme 4. Transformations of **14** to γ,γ-disubstituted cyclohexenones.



Scheme 5. Confirmation of the configuration of **17**.

In summary we have achieved the palladium-catalyzed asymmetric allylic alkylation of vinylogous thioesters in excellent yield and enantiomeric excess under neutral conditions. Both allyl enol carbonates and allyl β-ketoesters are competent substrates. However, the β-ketoesters react more sluggishly and therefore show a greater dependency on the choice of the 3-heteroatom substituent, to which the difference in the rate of decarboxylation is attributed. These compounds are readily transformed into γ,γ-disubstituted cycloalkenones, the utility of which will be demonstrated in synthetic endeavors in due course.

Experimental Section

Typical experimental procedures for the reaction of **13**: Two oven-dried test tubes were connected with a double-ended needle. One test tube was loaded with $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone; 5.2 mg, 0.005 mmol) and (*R*,*R*)-**7** (9.2 mg, 0.011 mmol), and the other tube was loaded with **13** ($R^2 = CH_3$; 0.20 mmol, 60.5 mg). The system was evacuated and flushed with argon three times, at which point dry degassed 1,4-dioxane (1.0 mL) was added to both of the test tubes. After being stirred for 20 min, the orange catalyst solution was transferred into the test tube containing the substrate. The color of the reaction solution turned to light yellow within a few minutes and then back to orange, thus indicating the completion of the reaction. The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel eluted with diethyl ether/petroleum ether (30:70, v/v) to afford **14** as a colorless oil (39 mg, 75 %).

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