Organocatalysis

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Organocatalytic Enantioselective Nucleophilic Vinylic Substitution**

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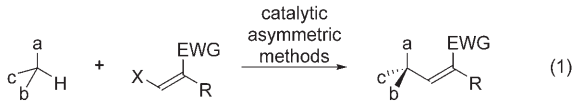
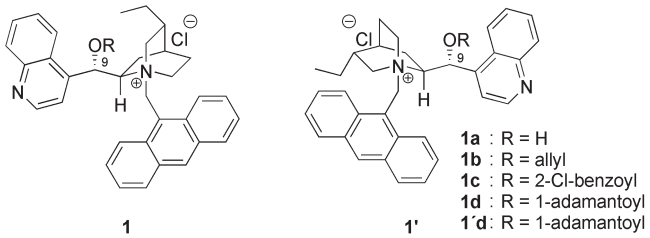
Many fundamental reactions in organic synthesis rely upon the use of enolates derived from carbonyl compounds as nucleophilic reaction partners. For this reason, the development of catalytic reaction protocols that result in the formation of enolates in chiral settings—thus enabling enantioselective transformations—must be considered a fundamental task for contemporary organic chemistry.[1]

Organocatalysis[2] has recently provided many fascinating examples of exquisite stereocontrol in C–C bond-forming reactions involving enolates. However, the majority of these lead to the formation of a bond between two sp^3-hybridized carbon atoms. Traditionally, the coupling of sp^3- and sp^2-hybridized carbon atoms has been a challenge and task for transition-metal-based catalytic systems,[3] and recently, examples of asymmetric α-arylations of carbonyl compounds have emerged.[4] However, despite the synthetic potential, there exist only a few reports that describe the coupling of vinylic compounds.[5] Furthermore, examples of such asymmetric reactions with electron-deficient alkenes [Eq. (1); EWG = electron-withdrawing group] have, to the best of our knowledge, been absent until now. Herein, we attempt to address this transformation by presenting the first catalytic enantioselective vinylic substitution reaction.



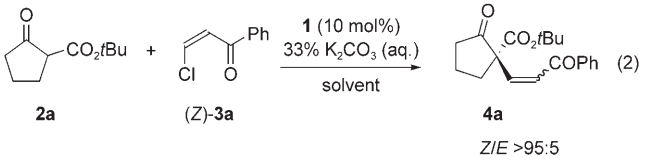
(1)

We envisioned that nucleophiles derived from 1,3-dicarbonyl compounds, such as β-ketoesters, could substitute a vinylic halide from activated β-haloalkenes through an addition–elimination (Ad_N–E) mechanism,[6] thereby forming a new C–C bond and an attractive vinyl-substituted all-carbon quaternary stereocenter. The complexation of the enolate with a chiral phase-transfer catalyst (PTC),[7] **1** or **1′**, derived from a cinchona alkaloid was anticipated to confer asymmetric induction to the reaction (Scheme 1). A major advantage of this protocol is the fact that vinylic substitutions on compounds such as **3**—readily prepared as the *Z* isomer from the corresponding alkyne[8]—often take place with complete retention of configuration of the C–C double bond.[9]



Scheme 1. Structures of phase-transfer catalysts derived from cinchonine (**1**) and from cinchonidine (**1′**).

Therefore, we set forward to identify suitable conditions for the reaction between (*Z*)-β-chloro-1-phenylpropenone ((*Z*)-**3a**) with alkyl cyclopentanone-2-carboxylates (e.g., **2a**), thus leading to **4a** [Eq. (2)]. A successful implementation of the strategy mentioned above would allow access to both geometric double-bond isomers, as the *Z*-configured products are readily isomerized to the more stable *E* configuration (see below). Initial screening (see the Supporting Information for the screening of ester groups, catalysts, and reaction conditions) revealed that the reaction did in fact proceed with virtually complete retention of the double-bond configuration. Furthermore, it was found that the combination of a PTC with a 9-anthracenylmethyl group[10] attached to the quinuclidine nitrogen atom and cyclopentanone 2-carboxylates **2** with bulky ester groups, such as *tert*-butyl, afforded promising levels of asymmetric induction. Table 1 shows further screening results. Catalysts **1b–d** (from dihydrocinchonine), substituted at 9-OH (Table 1, entries 2–4), performed better than the unsubstituted parent compound **1a** (Table 1, entry 1) both in terms of conversion and enantioselectivity.



The presence of a bulky 1-adamantoyl group in the catalyst (**1d**, obtained from **1a** under Schotten–Baumann conditions; see Supporting Information) proved to be optimal, and with this catalyst the reaction was readily carried out at −20 °C, thus affording the product (*Z*)-**4a** with 88 % *ee* (Table 1, entry 4). An exchange of the leaving group from chloride to bromide (Table 1, entry 5) afforded (*Z*)-**4a** with unchanged enantioselectivity, albeit at a slower rate.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Enantioselective vinylic substitution: Screening of catalysts and reaction conditions.[a]

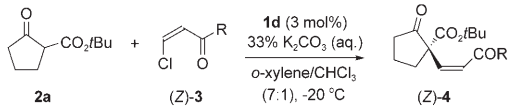
Entry	Cat.	Solvent	T [°C]	t [h]	Conv. [%][b]	*ee* [%][c]
1	**1a**	toluene/$CHCl_3$ (7:1)	0	4.3	25	57
2	**1b**	toluene/$CHCl_3$ (7:1)	0	4.5	87	74
3	**1c**	toluene/$CHCl_3$ (7:1)	0	4.0	61	82
4	**1d**	toluene/$CHCl_3$ (7:1)	−20	5.0	>95	88
5[d]	**1d**	toluene/$CHCl_3$ (7:1)	−20	5.5	50	88
6	**1d**	*o*-xylene	−20	6.0	88	89
7	**1d**	*o*-xylene/$CHCl_3$ (7:1)	−20	5.5	>95	91
8	**1d**[e]	*o*-xylene/$CHCl_3$ (7:1)	−20	13.5	>95	94

[a] Performed with (*Z*)-**3a** (0.12 mmol, 0.15 M) and **2a** (1.3 equiv). [b] Determined by ^{1}H NMR spectroscopic analysis. [c] The *ee* value of the *Z* isomer was determined by chiral stationary phase (CSP) HPLC. [d] Br as the leaving group instead of Cl. [e] Catalyst loading: 2.5 mol%.

Finally, it was found that high enantioselectivity—up to 94% *ee*—was obtained when changing the principal component of the reaction solvent to *o*-xylene instead of toluene (Table 1, entries 6 and 7), and most gratifyingly when the catalytic loading was decreased to 2.5 mol% (Table 1, entry 8).

Having established an optimal reaction protocol, we then explored the scope of the transformation with respect to both reaction partners. Various aromatic, heteroaromatic, and aliphatic β-halopropenones are suitable substrates for the catalytic reaction (Table 2, entries 1 and 3–9) and the products **4a**–**h** were obtained in good yields with enantioselectivities exceeding 90% *ee*. In all cases, the stereospecificity of the transformation was nearly complete—maintaining the *Z*-configured double bond (Table 2, entries 1 and 3–10). In a similar manner, the *E* product was obtained using (*E*)-**3a** as the substrate; however, the enantioselectivity was slightly decreased (Table 2, entry 2).

Table 2: Enantioselective vinylic substitution: Scope of disubstituted β-haloalkenes.[a]



2a (*Z*)-**3** (*Z*)-**4**

Entry	Substrate	R	Product	Yield [%][b]	Z/E[c]	*ee* [%][d]
1	**3a**	C_6H_5	**4a**	89 (92)	>95:5	94 (84)
2[e]	**3a**	C_6H_5	**4a**	85	<5:95	75
3	**3b**	4-$CF_3C_6H_4$	**4b**	89	>95:5	93
4	**3c**	4-$MeOC_6H_4$	**4c**	71	>95:5	93
5	**3d**	2-thienyl	**4d**	87	>95:5	91 (*S*)[f]
6	**3e**	1-naphthyl	**4e**	86	>95:5	94
7[g]	**3f**	Me[h]	**4f**	87	95:5	91 (*S*)[i]
8[j]	**3g**	$(CH_2)_2Ph$	**4g**	78	>95:5	93
9[j]	**3h**	*t*Bu	**4h**	90	>95:5	96
10[g]	**3i**	OEt	**4i**	77 (84)	>95:5	91 (81)

[a] Performed with **2a** (0.20 mmol, 0.15 M) and (*Z*)-**3** (1.1 equiv); the values in parenthesis were obtained with the catalyst derived from dihydrocinchonidine **1′d**. [b] Yield of the isolated product for both diastereomers. [c] Determined by ^{1}H NMR spectroscopic and HPLC analysis. [d] The *ee* value of the *Z* isomer was determined by CSP-HPLC. [e] (*E*)-**3a** was used. [f] The configuration was determined by X-ray analysis. [g] Method B was used (see Table 3). [h] Br as the leaving group. [i] The configuration was determined by chemical correlation. [j] Catalyst loading: 6 mol%.

Of special interest is the use of (*Z*)-**3f**, which is derived from 3-butyn-2-one, as the electrophilic reaction partner (Table 2, entry 7). The presence of both a *Z*-configured double bond and an enolizable methyl ketone in product (*Z*)-**4f**—formed in 87% yield with 91% *ee*—provides versatile functional handles for further synthetic manipulations.[11] Although less reactive, (*Z*)-**3i**, with an ester as the activating group, also undergoes the transformation to afford (*Z*)-**4i** with satisfactory results (Table 2, entry 10; 77% yield, 91% *ee*).

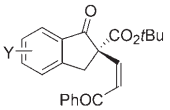
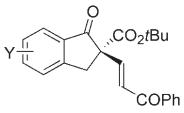
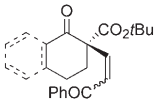
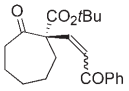
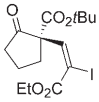
Further investigation of the reaction scope is presented in Table 3. Various cyclic β-ketoesters (Table 3, entries 1–3 and 5–7) undergo the vinylation with excellent selectivity. For example, a 1-indanone-derived β-ketoester with the ubiquitous 6,7-dimethoxy motif afforded product (*Z*)-**4l** in 95% yield with 95% *ee* (Table 3, entry 3). A similar result was also obtained for an *E*-alkene (Table 3, entry 4), thus giving (*E*)-**4l** in high yields, in good *E*/*Z* ratio, and with 97% *ee*; furthermore, this result shows that also the nucleophilic vinylic substitution for the *E*-alkenes (see also Table 2) maintains the configuration at the double bond. When the ring size is increased, slightly modified conditions (Table 3, method B, entries 5–7) are necessary as a result of the lower reactivity of the parent β-ketoesters. Interestingly, a slight drop in diastereoselectivity was also observed (compare Table 2, entry 1 with Table 3, entries 5 and 7), the possible origin of which is discussed below. Note, however, that in the case of product **4o** (entry 7) the *Z* and *E* isomers were easily separable by flash chromatography, thus allowing access to diastereomerically pure material.

An attempt to perform the reaction using noncyclic β-ketoesters revealed a limitation of the catalyst system described herein, as the products were obtained with less than 40% *ee*. Reactions were also carried out using the quasi-enantiomeric catalyst **1′d** (see Tables 2 and 3, values in parentheses) with consistent, although in some cases slightly lower, selectivities.

In the case of disubstituted alkenes, the vinylic substitution reaction can be regarded as a synthetic equivalent of the addition to electron-deficient triple bonds,[12] but with the advantages of yielding a wider range of compounds and being able to control the double-bond geometry of the products. The two reactions, however, being mechanistically distinct, imply that only the vinylic substitution affords the possibility of forming trisubstituted alkenes, for example, (*E*)-**4p**. As can be seen in entry 8 (Table 3), the α-iodine atom is easily tolerated in the catalytic reaction, affording the product with $E/Z > 95:5$[13] and 91% *ee*. In conjunction with cross-coupling methodology,[14] this reaction may provide a versatile platform for the synthesis of complex molecular structures. In this respect, it is important to note that **4p** was also prepared on a gram scale (81% yield, 1.67 g of **4p**, $E/Z > 95:5$, 91% *ee*).

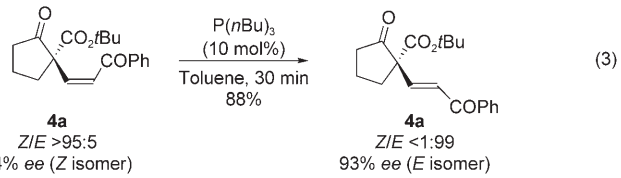
As mentioned above, easy access to both double-bond isomers of **4** can be gained through isomerization of the *Z*-configured double bond. For example, a catalytic amount of tri-*n*-butyl phosphine smoothly converts (*Z*)-**4a** into (*E*)-**4a** as

Table 3: Enantioselective vinylic substitution: Scope of nucleophiles and trisubstituted electrophiles.

Entry	Product	Y/Ph	Product	Yield [%][a]	Z/E[b]	*ee* [%][c]
1[d]		H	**4j**	90 (85)	>95:5 (>95:5)	90 (89)
2[d]		6-Cl	**4k**	96	>95:5	79
3[d]		6,7-$(MeO)_2$	**4l**	95	>95:5	95
4[d,e]		6,7-$(MeO)_2$	**4l**	94	<5:95	97[f]
5[g]		–	**4m**	77	90:10	89
6[g]		Ph	**4n**	96 (95)	95:5 (92:8)	95 (94)
7[h]		–	**4o**	81	86:14	75
8[g]		–	**4p**	74	<5:95	91[f]

[a] Yield of the isolated product for both diastereomers. [b] Determined by ^{1}H NMR spectroscopic and HPLC analysis. [c] The *ee* value of the *Z* isomers (except **4p**) was determined by CSP-HPLC. [d] Method A: β-ketoester (0.20 mmol, 0.15 M) and **3** (1.1 equiv), K_2CO_3 (33% aq.), *o*-xylene/$CHCl_3$ (7:1), and **1d** (3 mol%); the values in parentheses were obtained with the catalyst derived from **1′d**. [e] (*E*)-**3a** was used. [f] *E* isomer. [g] Method B: β-ketoester (0.20 mmol, 0.30 M), **3** (2.0 equiv), Cs_2CO_3 (66% aq.), *o*-xylene/$CHCl_3$ (7:1), and **1d** (6 mol%). [h] Method B, but with solid Cs_2CO_3.

shown in Equation (3). Alternatively, the *E* isomer of the products can be prepared directly by the catalytic reaction from (*E*)-**3** with moderate to excellent enantioselectivities (Table 2, entry 2 and Table 3, entry 4).

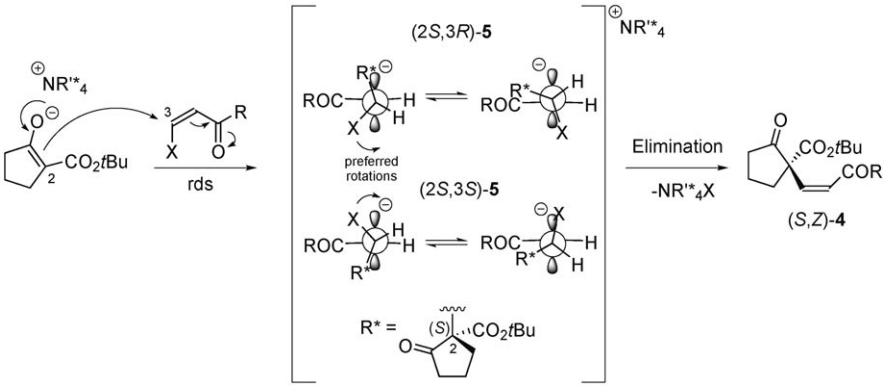


(3)

The overall substitution of the halide with retention of configuration can be rationalized through an Ad_N–E mechanism (Scheme 2).[15] Complexation of the enolate and the chiral PTC allows for the stereoselective addition to the α,β-unsaturated carbonyl compound in an initial rate-determining step. This addition results in the formation of a mixture of diastereomeric intermediates **5**, the composition of which cannot be ascertained as a result of their transient nature. Intermediates **5**, β-halo-substituted enolates, undergo rapid elimination of the leaving group to reform the C=C double bond. However, stereoelectronic effects demand the periplanar alignment of the enolate π orbital and the C–X σ* orbital for the elimination to be feasible. Such conformations can be achieved through either a short bond rotation (ca. 60°; indicated in Scheme 2) or a longer rotation (ca. 120°; not indicated). The preference for the short rotation (resulting in retention of configuration of the double bond) may be explained by the avoidance of destabilizing eclipsing interactions during the bond rotation[9a] and hyperconjugation between the electron-rich π system of the enolate and the σ* orbital of the C–X group.[9c]

Both diastereomeric intermediates in Scheme 2 eventually collapse to the same product, but the likely influence of the stereogenic center present at C2 in the elimination step is not considered in this preliminary model. The slight drop in diastereoselectivity (not as a result of product isomerization) observed for products **4m–o** may be trivially attributed to an overall (namely, in both diastereomeric intermediates) destabilization of the preferred rotational pathway. However, it may also originate from a difference among the two intermediates in the tendency to form products with retention of configuration. In the latter case, the key to obtaining very high diastereoselectivities for these more demanding substrates might be exquisite diastereocontrol of the initial addition reaction. This hypothesis is currently being tested in our laboratories.

In summary, we have presented the first example of a catalytic enantioselective vinylic substitution reaction. The reaction proceeds with high diastereoselectivity for both di- and trisubstituted alkenes and is carried out under experimentally simple conditions. Furthermore, we have presented new bulky phase-transfer catalysts that enable a highly enantioselective procedure.



Scheme 2. Proposed mechanism of the vinylic substitution reaction (rds = rate-determining step).

Experimental Section

Representative experimental procedure: **2a** (36.8 mg, 0.20 mmol), *o*-xylene/$CHCl_3$ (7:1, 1.3 mL), **3a** (36.7 mg, 0.22 mmol), and catalyst **1d** (3 mol%, 0.006 mmol, 4.1 mg) were added to a sample vial equipped with a magnetic stirring bar. The mixture was stirred for a short time at ambient temperature and then placed at −20 °C. When the mixture had cooled, a cold (−20 °C) solution of K_2CO_3 (33% aq., 0.6 mL) was added, and the biphasic mixture was vigorously stirred for 21 h, at which time the reaction was judged to be complete by TLC analysis. The organic phase was collected and the aqueous layer extracted with toluene (2 × 1 mL). The combined organic fractions were loaded onto SiO_2, and **4a** (55.2 mg, 0.176 mmol, 89% yield, $Z/E > 95:5$) was obtained by flash chromatography with Et_2O/CH_2Cl_2 (0:100–3:97) as the eluent.

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[13] Note that the change of *Z* to *E* selectivity is due to the iodine having a higher priority than the ester group according to the CIP system.
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[15] As noted by a referee, formation of alkynone intermediates in situ by dehydrohalogenation of **3** might also be a possible reaction pathway. Subjecting (*Z*)-**3b** to the reaction conditions resulted in the formation of trace amounts (< 5%) of the alkynone, only after prolonged reaction times (> 70 h). Furthermore, the reaction was carried out (with **2a**) using the corresponding alkynone under otherwise identical conditions. The result obtained (**4b**, $Z/E = 4:1$, 66/40% *ee*; compare with Table 2, entry 3) again suggests that alkynone intermediates are not involved.

