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Organocatalytic Enantioselective Nucleophilic Vinylic Substitution by α-Substituted-α-Cyanoacetates under Phase-Transfer Conditions

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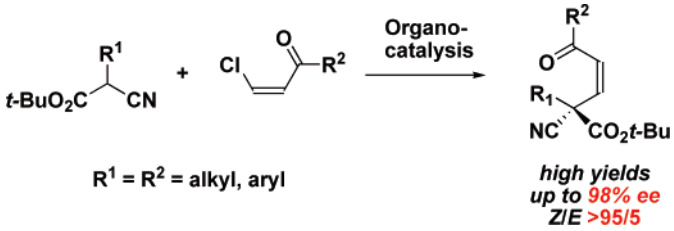

The organocatalytic enantioselective formation of vinyl-substituted all-carbon quaternary stereocenters via nucleophilic vinylic substitution by α-substituted-α-cyanoacetates is presented. The reaction proceeds well for different α-substituted-α-cyanoacetates and *β*-chloroalkenones using a dimeric cinchona alkaloid phase-transfer catalyst giving the products in good yield and with enantioselectivities up to 98% ee.

Introduction

The conjugate addition of enolates to α,*β*-unsaturated carbonyl systems, that is, the Michael reaction, is a fundamental C−C bond forming reaction in organic chemistry. Due to its importance, asymmetric variants of the Michael reaction have been of great interest, which have resulted in continuous attention from the synthetic community. The strides of many research groups have resulted in the development of chiral metal complexes or chiral secondary amines that are capable of catalyzing the Michael reaction with high stereoselectivities.[1]

Activated methine compounds, such as *β*-ketoesters, are interesting nucleophiles in relation to the Michael reaction because upon addition of the electrophile an all-carbon quaternary stereocenter is constructed.[2] However, a particular class of activated methine compounds—the α-substituted-α-cyanoacetates—has, until recently, been problematic to encompass as nucleophiles in asymmetric Michael reactions. This issue was explicitly pointed out by Grossman et al. in their paper, describing the use of phosphoamidites as catalysts for this reaction: "Michael reactions of α-cyano esters are among the most difficult to render asymmetric".[3] However, recently, two powerful catalytic systems finally overcoming the problem have been devised. Jacobsen et al. have employed chiral metal−salen complexes to achieve a stereoselective Michael reaction using α-substituted-α-cyanoacetates as the nucleophiles,[4] while Deng et al. have developed a class of cinchona alkaloid-derived bifunctional chiral base catalysts to effect the Michael reaction between α-substituted-α-cyanoacetates and various Michael acceptors.[5]

The interest in employing these nucleophiles in asymmetric reactions is understandable when considering the synthetic possibilities associated with having both an ester and nitrile functionality attached to the same chiral carbon atom. In this paper, we wish to advance the synthetic methodology centered around asymmetric conjugate additions of α-substituted-α-cyanoacetates **1** by demonstrating that their nucleophilic addition

(1) For reviews on asymmetric Michael reactions, see: (a) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapters 31.1 and 31.2. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

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(3) (a) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871. For an isolated successful example of an asymmetric Michael reaction involving α-substituted-α-cyanoacetates using a chiral Rh complex as the catalyst, see: (b) Sawamura, M.; Himashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.

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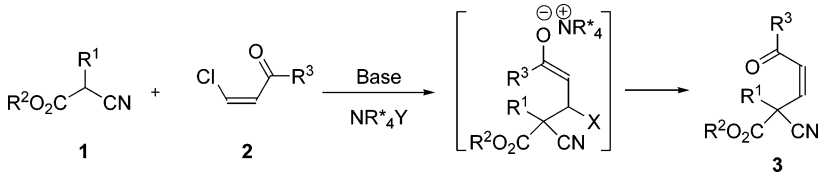
SCHEME 1. Organocatalytic Enantioselective Nucleophilic Vinylic Substitution by α-Substituted-α-Cyanoacetates



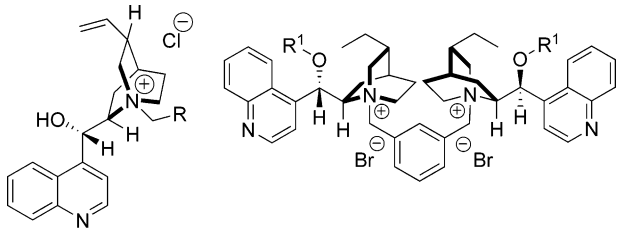
to β-halo-α,β-unsaturated carbonyl compounds **2** can lead to the stereoselective construction of all-carbon quaternary stereocenters appended with an electron-deficient vinyl group[6] **3** by the formal substitution of the vinylic halide (Scheme 1).[7]

Mechanistically, the vinylic substitution reaction occurs by initial conjugate addition of the nucleophile to the α,β-unsaturated carbonyl compound, resulting in the formation of a β-halo-substituted enolate (Scheme 1) which undergoes rapid elimination of the halide re-forming the α,β-unsaturated system. Most importantly, this type of addition−elimination reaction often takes place with retention of configuration at the C−C double bond due to the stereoelectronic properties of the intermediate β-haloenolate.[8]

Realizing the necessity of a stoichiometric base to remove the acid formed during the reaction made us turn our attention to phase-transfer catalysis[9] as the catalytic method of choice. Serving as an inspiration in this respect was the fact that we could find no examples in the literature describing the successful use of **1** in conjunction with a chiral phase-transfer catalyst (PTC), and in fact, we were unable to find any reports describing catalytic enantioselective nucleophilic substitution reactions of any kind employing **1** as the nucleophile.[10]

Results and Discussion

Chiral PTCs **4a**−**d** derived from cinchonine were used to induce chirality in the reaction between α-substituted-α-cyanoacetates **1** and (*Z*)-β-chloroalkenones **2** (Scheme 1). We were pleased to note, in the initial screening, that not only did the vinylic substitution reaction proceed cleanly to give **3** when cinchonine-derived catalysts **4a**−**d** were employed, but that good control of the double-bond geometry was also possible, leading to retention of the (*Z*)-configuration. Therefore, both geometric double-bond isomers of the product **3** can be efficiently accessed as the (*Z*)-configured products are easily isomerized to the more stable (*E*)-configuration (see below).



4a: R = phenyl
4b: R = anthracene

4c: R^1 = H
4d: R^1 = allyl

A study of the structural requirements of the cinchona backbone was carried out to determine the optimal catalyst architecture, along with the most suitable conditions for the reaction of **1a** with (*Z*)-**2a** (eq 1, Table 1). Although enantiomeric excess could be obtained with simple cinchonine-derived PTCs (**4a**,**b**) (entries 1 and 2), it was realized that enhanced asymmetric induction was possible when a catalyst (**4c**) employing two units of cinchonine joined via a *m*-xylene bridging unit was used (entries 3−7).[11] When using this catalyst, $CHCl_3$ and Cs_2CO_3(aq) were found to be the optimal solvent and base. A useful increase in enantiomeric excess was also observed when lower temperatures were used. Pleasingly, protecting the 9-hydroxy group on the cinchona backbone with an allyl group (**4d**) led to higher enantioselectivity (entry 8) than with the parent structure (**4c**), and in all cases, only 3 mol % of PTC was needed to obtain excellent conversion at the stated temperature. The use of α-substituted-α-cyanoacetates bearing *tert*-butyl ester groups was found to be essential to gain good levels of enantiocontrol.

Once the reaction conditions had been established, we moved on to examine the scope of the reaction regarding the electrophilic reaction species (eq 2, Table 2). The standard reaction conditions could be applied to (*Z*)-β-chloro-1-arylpropenones bearing both electron-poor (**2b**) and electron-rich (**2c**) aryl ketones (entries 2 and 3), with comparable results to those obtained for **2a** (entry 1), although in the case of the electron-poor system, the enantioselectivity obtained was lower (75% ee, compared to 93% ee for **2a**). Heteroaromatic substituted electrophiles were tested by using (*Z*)-β-chloro-1-thiophenepropenone **2d**, giving high yields and enantioselectivity (95%, 97% ee, entry 4). The 1-naphthyl-substituted electrophile (**2e**) worked less well, only giving 43% ee and *Z*/*E* 88/12 (entry 5). It is

(6) Construction of this type of quaternary stereocenter has only been successful in a few cases: (a) Hajos, Z.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (d) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672.

(7) We have recently developed catalytic systems enabling this transformation for cyclic 1,3-dicarbonyl compounds; see: (a) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *39*, 6551. (b) Poulsen, T. B.; Bernardi, L.; Aléman, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem.* Soc. **2007**, *129*, 441.

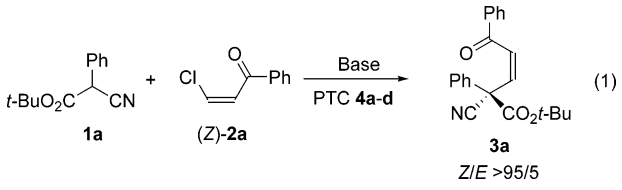
(8) (a) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73. (b) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211. (c) Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* **1979**, *101*, 5095.

(9) For reviews on asymmetric phase-transfer catalysis, see: (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 727. For examples of phase-transfer-catalyzed asymmetric reactions constructing all-carbon quaternary stereocenters, see: (b) Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (c) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (d) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549. (e) Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191.

(10) For enantioselective aliphatic nucleophilic substitutions using chiral auxiliaries, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1445. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 261. (c) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *Synlett* **1994**, 302. (d) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *Tetrahedron* **1994**, *50*, 9837. (e) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *J. Org. Chem.* **1994**, *59*, 2497. (f) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A. *Tetrahedron* **1995**, *51*, 5921. (g) Cativiela, C.; Diaz-de-Villegas, M. D.; Calvez, J. A.; Lapena, Y. *Tetrahedron* **1997**, *53*, 5891.

(11) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.

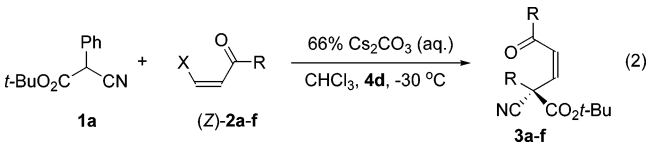
TABLE 1. Screening of Reaction Conditions for the Organocatalytic Enantioselective Vinylic Substitution Reaction[a]



entry	conditions	conv (%)[b]	ee (%)[c]
1[d]	**4a**, toluene, −20 °C	99	30
2[d]	**4b**, toluene, −20 °C	99	49
3[d]	**4c**, toluene, −20 °C	82	58
4[d]	**4c**, CH_2Cl_2, −20 °C	99	76
5[d]	**4c**, $CHCl_3$, −20 °C	99	80
6[e]	**4c**, $CHCl_3$, −20 °C	99	83
7[e]	**4c**, $CHCl_3$, −35 °C	99	86
8[e]	**4d**, $CHCl_3$, −35 °C	99	93

[a] Performed with 0.1 mmol **1a** (0.5 M), 1.3 equiv of (*Z*)-**2a** and 3 mol % of **4a**−**d**. [b] Determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess of the (*Z*)-isomer determined by CSP-HPLC. [d] 33% K_2CO_3(aq) used as base. [e] 66% Cs_2CO_3(aq) used as base.

TABLE 2. Reaction of *tert*-Butyl α-Phenyl-α-Cyanoacetate 1a with Various (*Z*)-*β*-Halo-1-Propenones 2a−f[a]



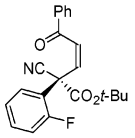
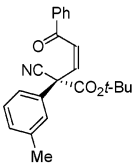
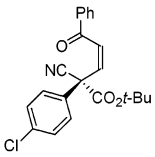
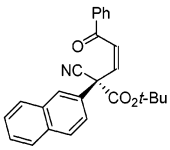
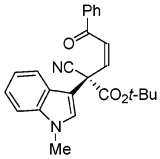
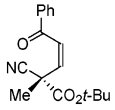
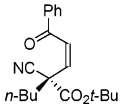
entry	R	X	yield (%)[b]	*Z*/*E*[c]	ee (%)[d]
1[e]	C_6H_5, **2a**	Cl	95, **3a**	99/1	(−)-93
2	4-CF_3−C_6H_4, **2b**	Cl	99, **3b**	97/3	(−)-75
3	4-MeO−C_6H_4, **2c**	Cl	92, **3c**	97/3	(−)-95
4	2−thienyl, **2d**	Cl	95, **3d**	97/3	(−)-97[f]
5[g]	1−naphthyl, **2e**	Cl	93, **3e**	88/12	(−)-43
6[g]	Me, **2f**	Br	99, **3f**	95/5	(−)-38

[a] Method A: 0.2 mmol **1a** (0.5 M), 1.2 equiv of (*Z*)-**2a**−**f**, and 3 mol % of **4d**. [b] Isolated yield of both diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of the (*Z*)-isomer determined by CSP-HPLC. [e] At −35 °C. [f] The absolute configuration was assigned to be (*R*) by single-crystal X-ray analysis. [g] Method B: 0.20 mmol of **1a**, 2 equiv of (*Z*)-**2f**, and 6 mol % of **4d**.

possible that the lowering of the enantioselectivity and the decrease in double-bond geometry control are due to the increased steric bulk this electrophile brings to an already congested area of the reaction product **3e**. Unfortunately, the catalytic reaction is unable to cope well with the use of (*Z*)-*β*-bromo-1-alkylpropenones, giving 38% ee, albeit with high yield (99%, entry 6). It should be noted that, in all cases (except entry 5), control of the configuration of the double-bond was excellent (at least *Z*/*E* 95/5).

The range of nucleophilic α-substituted-α-cyanoacetates able to take part in this reaction was then examined (Table 3). As well as the standard *tert*-butyl α-phenyl-α-cyanoacetate **1a** (Table 2, entry 1; 95% yield, 93% ee), various α-substituted-α-cyanoacetates bearing both aromatic (**1b**−**f**, entries 1−5) and alkyl (**1g**,**h**, entries 6 and 7) substituents were useful partners in this new catalytic reaction, giving good yields (75−99%) and enantioselectivities (76−98% ee). In all examples, the stereospecificity of the transformation is high (at least *Z*/*E* >95/5). The α-alkyl-α-cyanoacetates were slightly less reactive than the analogous α-aryl compounds, requiring the use of twice as much catalyst (6 mol % rather than 3 mol %) and 2 equiv of

TABLE 3. Scope of α-Substituted-α-Cyanoacetates 1b−h[a]

entry	product	yield (%)[b]	*Z*/*E*[c]	ee (%)[d]
1		80 - **3g**	>95/5	(-)-84
2		97 - **3h**	99/1	(-)-92
3		92 - **3i**	99/1	(-)-90
4		99 - **3j**	98/2	(-)-94
5		86 - **3k**	>95/5	(-)-98
6[e]		95 - **3l**	99/1	(-)-92
7[e]		75 - **3m**	>95/5	(-)-76

[a] Method A: 0.20 mmol of **1b**−**f** and 1.2 equiv of **2a**, 66% Cs_2CO_3(aq), $CHCl_3$ (0.5 M), −30 °C, 3 mol % of **4d**. [b] Isolated yield of both diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Of the (*Z*)-isomer determined by CSP-HPLC. [e] Method B: 0.20 mmol of **1g**,**h** and 2 equiv of **2a**, 66% Cs_2CO_3(aq), $CHCl_3$ (0.5 M), −30 °C, 6 mol % of **4d**.

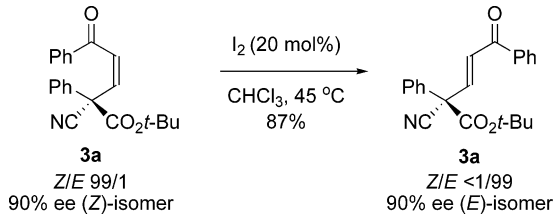
(*Z*)-*β*-chloro-1-phenylpropenone **2a**. However, the general reaction conditions were the same.

The isomeric substrate (*E*)-**2a** was also expected to undergo the vinylic substitution. In this case, the reaction led to complete retention of the double-bond geometry (*E*/*Z* >99/1). However, the enantiocontrol (24% ee) decreased significantly under the same reaction conditions.[12] However, the (*Z*)-configured products can easily be converted into the (*E*)-configured isomer by reaction with catalytic amounts of iodine, giving 87% yield and complete fidelity of enantiomeric excess (Scheme 2).[13]

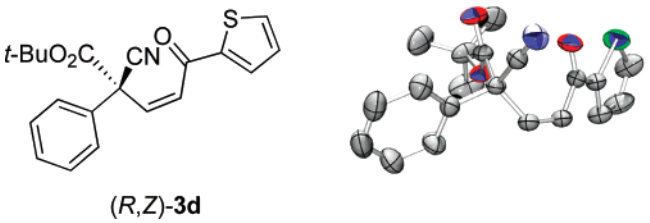
(12) Yield was 96%, *E*/*Z* >99/1, 24% ee.

(13) The use of tri-*n*-butyl phosphine as the isomerization catalyst should be avoided as it leads to a racemic mixture of the (*E*)-product. This is due to the stability of the α-substituted-α-cyanoacetate anions as leaving groups.

SCHEME 2. Isomerization of (*Z*)-3a to (*E*)-3a Using Catalytic Iodine



The absolute configuration of the stereocenter formed was established to be (*R*) by examination of a single-crystal X-ray structure obtained using (*Z*)-*β*-chloro-1-thiophenepropenone (*Z*)-**2d** as the electrophilic partner in the nucleophilic vinylic substitution reaction (Figure 1).[14]



(*R*,*Z*)-**3d**

FIGURE 1. X-ray structure of (*R*,*Z*)-**3d**. Hydrogen atoms are omitted for clarity.

Conclusion

In summary, we have demonstrated that the organocatalytic nucleophilic vinylic substitution reaction of α-substituted-α-cyanoacetates with (*Z*)-*β*-chloro-1-arylpropenones can be carried out under PTC conditions, forming a vinyl-substituted quaternary stereocenter with four distinct functional groups. The described reaction is operationally simple to perform and proceeds with good yield, high enantiomeric excess, and excellent control of the double-bond geometry.

(14) By analogy with HPLC traces and optical rotations, the same configuration (*R*) for the products **3a**−**c**,**e**−**k** and the opposite (*S*) (due to a change in the priority of the groups according to the CIP system) for **3l**,**m** could be inferred.

Experimental Section

Representative Experimental Description for the Catalytic Enantioselective Vinylic Substitution Reaction. (*R*,*Z*)-2-Cyano-5-oxo-2,5-diphenylpent-3-enoic Acid *tert*-Butyl Ester (3a). *tert*-Butyl α-phenyl-α-cyanoacetate **1a** (0.2 mmol) was added to a stirring bar equipped test tube and dissolved in $CHCl_3$ (0.4 mL). (*Z*)-*β*-Chloroalkene **2a** (0.24 mmol) and catalyst **4d** (3 mol %) were added, and the resulting mixture was cooled to −35 °C before 0.4 mL of precooled 66% Cs_2CO_3(aq) was added. The reaction was stirred at this temperature for 19 h before the organic phase was passed through a plug of silica and the reaction mixture eluted with Et_2O. The pure product **3a** was obtained by FC using petroleum ether/Et_2O 20:1 to remove the electrophile followed by a 4:1 mixture of the same solvents to give **3a** (66 mg, 95% yield, *Z*/*E* 99/1): ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, dd, J = 3.8, 5.7 Hz), 7.66 (2H, m), 7.59 (1H, m), 7.48 (2H, t, J = 7.6 Hz), 7.41 (3H, m), 7.26 (1H, d, J = 11.4 Hz), 6.52 (1H, d, J = 11.4 Hz), 1.38 (9H, s); ^{13}C NMR ($CDCl_3$) δ 189.7, 164.7, 141.1, 137.3, 136.7, 133.8, 129.3, 129.0, 128.9, 128.8, 128.3, 126.6, 116.8, 84.8, 54.4, 27.7; HRMS calcd for $C_{22}H_{21}NO_3$ $[M + Na]^+$, 370.1419; found, 370.1414; $[\alpha]_D^{20}$ −130.3 (c = 1.0, CH_2Cl_2, 93% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate = 1.0 mL/min; τ_{major} = 19.4 min, τ_{minor} = 24.3 min (93% ee).

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Supporting Information Available: Complete experimental procedures, characterization data for all new compounds, and stereochemical proof. This material is available free of charge via the Internet at http://pubs.acs.org.

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