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Kinetic resolution of 5-substituted cycloalkenones by peptidic amidophosphane-copper-catalyzed asymmetric conjugate addition of dialkylzinc

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Abstract—Asymmetric conjugate alkylation reaction of racemic 5-substituted cyclohexenones with dialkylzinc reagents was catalyzed by 2–5 mol % of dipeptidic amidophosphane-Cu(MeCN)$_4$BF$_4$ in toluene at 0 °C for 20 min to recover enantioenriched starting 5-substituted cyclohexenones with 88–98% ee in 28–41% yield along with trans major 3-alkylated 5-substituted cyclohexanones with 81–90% ee in 53–60% yield. Complete consumption of starting racemic 5-TMS-cyclohexenone by treating with diethylzinc under the catalytic asymmetric reaction conditions gave trans major 85:15 mixture of *trans*- and *cis*-3-ethyl-5-TMS-cyclohexanones with 15% ee (for trans) in 83% combined yield, indicating that the conformation-controlled trans-alkylation of cyclohexenone prevails over chiral catalyst-controlled enantiofacial differentiation.
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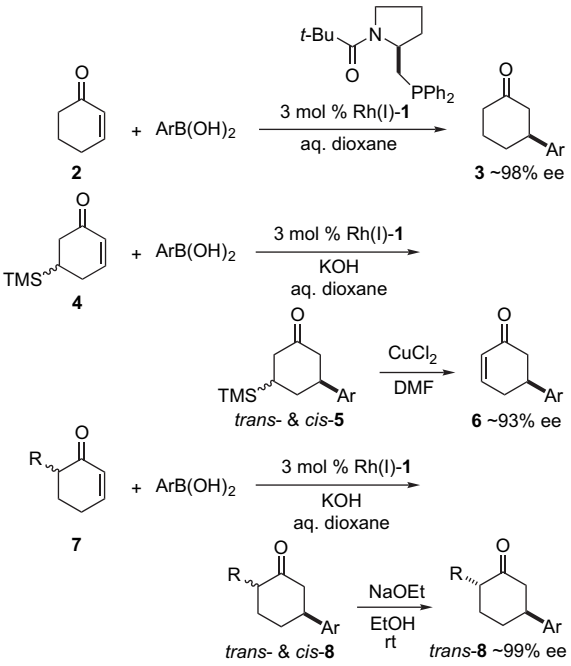
1. Introduction

The catalytic asymmetric conjugate addition reaction of organometallic reagents with olefins activated by an electron withdrawing group has been the subject of recent energetic researches.[1] The application of the catalytic asymmetric reaction into the kinetic resolution of racemic enones has been also the subject of extended researches.[2] We have been involved in this fascinating field by applying a chiral amidophosphane as a chiral ligand for copper and rhodium metals. Our accomplishments are visualized by the chiral amidophosphane **1**-rhodium-catalyzed asymmetric conjugate arylation of arylboronic acids with cyclohexenone **2** giving **3** with high enantioselectivity (Scheme 1).[3] Racemic 5-TMS-cyclohexenone **4** has been also a substrate applicable in the asymmetric conjugate arylation to provide highly enantioselective synthesis of 5-aryl-cyclohexenones **6** through oxidative detrimethylsilylation of **5**, obtained by a chiral ligand **1**-controlled enantioselective arylation of **4**.[4] Racemic cyclohexenones **7** bearing a substituent at the 6-position have been good substrates to give *trans*-3,6-disubstituted cyclohexanones **8** with extremely high enantioselectivity through epimerization of a mixture of *trans*- and *cis*-**8**.[5] It is important to pay attention to the fact that the substrate-controlled trans-arylation of **4** and **7** was surmounted by the chiral catalyst-controlled enantiofacial differentiating control, giving a mixture of nearly equal amounts of trans- and cis-products.[6]



Scheme 1. Rhodoium-catalyzed asymmetric conjugate arylation of **2**, **4**, and **7** with arylboronic acids.

The copper(I)-catalyzed asymmetric conjugate alkylation of cyclohexenone **2** with dialkylzinc reagents has been one of our recent successes giving 3-alkylcyclohexanones **10** with satisfactorily high enantioselectivity of up to 98% ee (Scheme 2).[7] The success is critically relied on the

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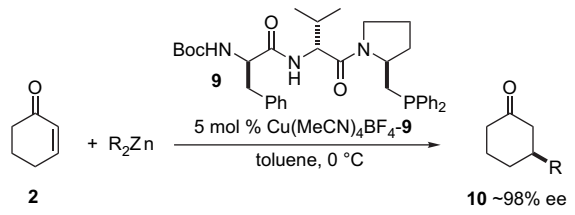
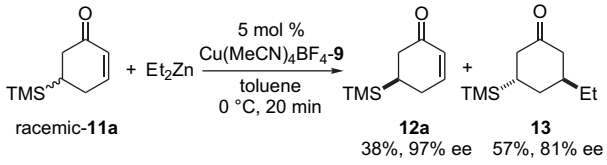
development of a dipeptide-connected amidophosphane **9**[8] obtained by the modification of **1** that mediated production of **10** with a miserably poorer ee.[9]



Scheme 2. Copper(I)-**9**-catalyzed asymmetric conjugate alkylation of cyclohexenone **2** with dialkylzinc reagents.

The kinetic resolution of racemic compounds to enantiopure ones has been the target of copper-catalyzed asymmetric conjugate addition reactions.[10,11] It is natural for us to apply the **9**-copper(I)-catalyzed asymmetric alkylation reaction of **2** with dialkylzinc reagents into the catalytic kinetic resolution of 5-substituted cyclohexenones **11** (Scheme 3). We describe herein that the catalytic kinetic resolution of racemic **11** was successfully carried out by applying the catalytic asymmetric alkylation reaction to provide enantioenriched **12** with high ee of up to 98% ee. It is also important to note that the substrate-controlled trans-alkylation is operative in this reaction, contrary to the chiral ligand-controlled enantioface differentiating arylation as has been observed in the reactions of **4** to **5**, and **7** to **8**.



Scheme 3. Catalytic kinetic resolution of racemic **11a**.

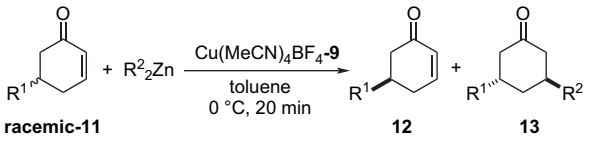
2. Results and discussion

2.1. Catalytic kinetic resolution of 5-substituted cyclohexenones

The copper(I)-**9**-catalyzed asymmetric conjugate alkylation reaction was applied in the catalytic kinetic resolution of 5-substituted cyclohexenones **11**, which, in enantioenriched forms **12**, are versatile chiral building blocks of some natural products and the biologically potent compounds.[2,9] The reaction of racemic 5-TMS-cyclohexenone **11a** (R^1=TMS) with 1.2 equiv of diethylzinc under the catalysis of 5 mol % of **9**-Cu(I) in toluene at 0 °C for 20 min gave trans-ethylation product **13** (R^1=TMS, R^2=Et) with 81% ee in 57% yield and recovered enantioenriched starting (*R*)-**12a** (R^1=TMS) with 97% ee in 38% yield (Scheme 3, Table 1, entry 1).[12] The absolute configuration of **12a** was determined by the specific rotation,[12] and hence the configuration of **13** was deduced.

The catalytic isopropylation of **11a** with diisopropylzinc gave *trans*-**13** (R^1=TMS, R^2=*i*-Pr) with 86% ee in 66% yield and recovered (*R*)-**12a** with 96% ee in 28% yield (entry 2). These two sets of reactions well indicate that the kinetic resolution of racemic **11** is promising.

Table 1. Catalytic kinetic resolution of racemic 5-substituted cyclohexenones **11**[a]



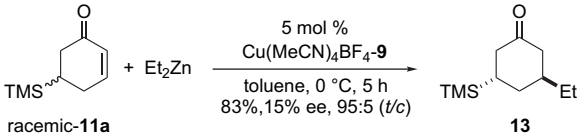
Entry	11	R^1	12			13		
			R^2	Yield %	ee %	Yield %	ee[c] %	trans/cis
1[a]	**11a**	TMS	Et	38	97	57	81	99/1
2[a]	**11a**	TMS	*i*-Pr	28	96	66	86	95/5
3[b]	**11b**	Me	Et	38	98	58	87	98/2
4[b]	**11c**	Ph	Et	41	88	53	87	93/7
5[b]	**11d**	2-Naph	Et	33	95	64	90	87/13

[a] Catalyst loading was 5 mol %.
[b] Catalyst loading was 2 mol %.
[c] For *trans*-**13**.

Thus, 5-methyl-, 5-phenyl, and 5-(naphth-2-yl)cyclohexenones **11b–d** were good substrates for the **9**-Cu(I)-catalyzed kinetic resolution, recovering enantioenriched starting (*R*)-cyclohexenones **12b–d** with 98%, 88%, and 95% ees in reasonably good recovery yields (entries 3–5). It is also important to note that the kinetic resolution was catalyzed by 2.6 mol % of amidophosphane **9** and 2 mol % of copper(I) tetrafluoroborate.

2.2. Enantiofacial selection by chiral catalyst control versus trans-alkylation by substrate control

Trans-alkylation is the major course in the catalytic kinetic resolution of **11**, producing stereoselectively *trans*-**13** and recovering **12** with high ees as summarized in Table 1. Stereochemically unique point of these substituted cyclohexenones is the substrate-based stereochemical control, that is, directing trans-alkylation due to the preferred axial attack to cyclohexenone moiety.[13] The complete consumption of racemic 5-TMS-cyclohexenone **11a** by using 2 equiv of diethylzinc at 0 °C for 5 h gave a trans major 95:5 mixture of *trans*- and *cis*-**13a** with 15% ee (for *trans*-**13**) in 83% yield. This indicates that trans-alkylation by the substrate control prevails the chiral catalysis control (Scheme 4).



Scheme 4. Complete consumption of racemic **11a** to trans major **13**.

3. Conclusion

A highly enantioselective catalytic kinetic resolution of 5-substituted cyclohexenones has been developed by using the chiral dipeptide-connected amidophosphane-copper(I)-catalyzed conjugate alkylation reaction with dialkylzinc reagents. Key to these efficient enantioselective catalytic kinetic resolution is a dipeptidic amidophosphane ligand

for copper(I). However, cyclohexenone-controlled transalkylation prevails the chiral ligand-copper(I) catalyst-controlled enantiofacial differentiation, while chiral catalyst control surmounted cyclohexenone control in the amidophosphane-rhodium(I)-catalyzed conjugate arylation.

4. Experimental

4.1. General

Melting points are uncorrected. Reaction was carried out under Ar. Silica gel column chromatography was used for purification. IR spectra were expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shift values are expressed in parts per million relative to internal TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The starting enones **11a–d** were prepared according to the procedures reported.[14]

4.1.1. Kinetic resolution of racemic 5-trimethylsilylcyclohexenone 11a (R^1=TMS) to (−)-(*R*)-12a (R^1=TMS) with diethylzinc (Table 1, entry 1). A suspension of dipeptidic amidophosphane **9** (39.9 mg, 0.065 mmol) and $Cu(MeCN)_4BF_4$ (15.9 mg, 0.05 mmol) in 18.5 mL toluene was stirred to form a solution at rt for 1 h. A solution of racemic **11a** (R^1=TMS) (1.0 mmol) in 13 mL of toluene was added at rt. A hexane solution of diethylzinc (1.2 mL, 1.2 mmol) was then added at 0 °C and the whole was stirred at 0 °C for 20 min. The reaction was quenched with 10% HCl and stirred at rt for 0.5 h. The organic layer was separated and the water layer was extracted with diethyl ether. The combined organic layers were washed with satd sodium bicarbonate and brine, and then dried over sodium sulfate. Concentration and chromatography (hexane/diethyl ether=20:1) gave (−)-*trans*-3-ethyl-5-trimethylsilylcyclohexanone **13** (R^1=TMS, R^2=Et) (112 mg, 57% yield, 81% ee) as a colorless oil of $[\alpha]_D^{25}$ −52.3 (*c* 1.13, $CHCl_3$) and (−)-(*R*)-5-trimethylsilylcyclohexenone **12a** (R^1=TMS) (62 mg, 38% yield, 97% ee) as a colorless oil of $[\alpha]_D^{25}$ −9.21 (*c* 1.26, $CHCl_3$).

(−)-*trans*-**13** (R^1=TMS, R^2=Et):[10] The ee was determined to be 81% by GC (β-Dex 325, 30 m×0.25 mm×0.25 mm, 100 °C, major 31 min and minor 29 min). ^1H NMR: 0.00 (9H, s), 0.87 (3H, t, *J*=7.4 Hz), 1.26–2.49 (10H, m). ^{13}C NMR:−3.67, 11.6, 25.7, 29.3, 39.5, 42.0, 46.5, 213.2. IR (neat): 1740. EIMS *m*/*z*: 198 (M^+).

(−)-(*R*)-**12a**:[12b] The ee was determined to be 97% by GC (γ-Dex 325, 30 m×0.25 mm×0.25 mm, 100 °C, major 24.2 min and minor 28.5 min). The absolute configuration was determined to be *R* by the specific rotation.

4.1.2. (−)-3-Isopropyl-5-trimethylsilylcyclohexanone 13 (R^1=TMS, R^2=*i*-Pr) (entry 2). A colorless oil of $[\alpha]_D^{25}$ −17.1 (*c* 1.09, $CHCl_3$). The trans isomer was determined to have 86% ee by GC (β-Dex 325, 30 m× 0.25 mm×0.25 mm, 110 °C, major 28 min and minor 29 min). The trans/cis ratio was determined to be 95:5 by the integration area of ^{13}C NMR. ^1H NMR: 0.00 (9H, s), 0.86 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.9 Hz), 1.21 (1H, m), 1.51–2.38 (8H, m). ^{13}C NMR:−3.67, 18.9 (cis), 19.2 (cis), 20.0 (trans), 20.4 (trans), 21.4 (trans), 26.9 (cis), 28.0 (trans), 29.3 (trans), 29.4 (cis), 32.8 (cis), 41.7 (trans), 42.0 (cis), 44.0 (trans), 44.7 (trans), 45.0 (cis), 48.8 (cis), 217.7 (trans). IR (neat): 1710. EIMS *m*/*z*: 212 (M^+). HRMS *m*/*z* calcd for $C_{12}H_{24}SiO$: 212.1596. Found: 212.1589.

4.1.3. (−)-(*R*)-5-Methylcyclohexenone 12b (R^1=Me) (entry 3). Chromatography (hexane/diethyl ether=10:1) gave a 98:2 trans/cis mixture of (−)-3-ethyl-5-methylcyclohexanone **13** (R^1=Me, R^2=Et)[2a] (164 mg, 58% yield, 87% ee (trans)) as a colorless oil of $[\alpha]_D^{25}$ −1.10 (*c* 2.18, $CHCl_3$) and (−)-(*R*)-**12b**[15] (38 mg, 38% yield, 98% ee) as a colorless oil of $[\alpha]_D^{25}$ −88.0 (*c* 0.93, $CHCl_3$).

(−)-**13** (R^1=Me, R^2=Et): Major *trans*-**13** was determined to have 87% ee by GC (β-Dex 325, 30 m×0.25 mm×0.25 mm, 80 °C, major 25 min and minor 32 min). The trans/cis ratio was determined to be 98:2 by the integration area of ^1H NMR signals of the trans Me (d) and the cis Me (d). ^1H NMR: 0.89 (3H, t, *J*=7.6 Hz, trans+cis), 0.98 (0.98H, d, *J*= 6.7 Hz, trans), 1.03 (0.2H, d, *J*=6.4 Hz, cis), 1.32 (2H, m, trans+cis), 1.57–1.66 (2H, m, trans+cis), 1.93–2.11 (3H, m, trans+cis), 2.23 (1H, m, trans+cis), 2.39–2.42 (2H, m, trans+cis). ^{13}C NMR: 11.0 (cis), 11.4 (trans), 20.7 (trans), 22.3 (cis), 27.7 (trans), 29.5 (trans), 31.1 (cis), 33.1 (cis), 36.2 (trans), 37.1 (trans), 39.7 (cis), 40.1 (cis), 46.7 (trans), 47.1 (cis), 48.9 (trans), 49.7 (cis), 212.3 (trans). IR (neat): 1710. EIMS *m*/*z*: 140 (M^+).

(−)-(*R*)-**12b**: The ee was determined to be 98% by GC (β-Dex 325, 30 m×0.25 mm×0.25 mm, 70 °C, major 35 min and minor 34 min). The absolute configuration was determined by the specific rotation.

4.1.4. (−)-(*R*)-5-Phenylcyclohexenone 12c (R^1=Ph) (entry 4). Chromatography (hexane/diethyl ether=20:1) gave a 93:7 trans/cis mixture of (+)-**13** (R^1=Ph, R^2=Et)[10] (107 mg, 53% yield, 87% ee (trans), 92% ee (cis)) as a colorless oil of $[\alpha]_D^{25}$ +19.3 (*c* 1.08, $CHCl_3$) and (−)-*R*-**12c**[10] (71 mg, 41% yield, 88% ee) as a colorless oil of $[\alpha]_D^{25}$ −39.0 (*c* 1.02, $CHCl_3$).

(+)-**13** (R^1=Ph, R^2=Et): Major *trans*- and *cis*-**13** were determined to have 87% ee and 92% ee by HPLC (Daicel Chiralcel AD-Hx2, hexane/*i*-PrOH=20:1, 0.5 mL/min, 254 nm, trans: major 25 min and minor 28 min, cis: major 30 min and minor 27 min). The trans/cis ratio was determined to be 93:7 by the integration area of ^1H NMR signals of the trans Me (t) and the cis Me (t). ^1H NMR: 0.89 (0.93H, t, *J*=7.4 Hz, trans), 0.93 (0.07H, t, *J*=7.4 Hz, cis), 1.34–1.46 (2H, m, trans+cis), 1.92–2.07 (3H, m, trans+cis), 2.23 (1H, m, trans+cis), 2.53–2.64 (3H, m, trans+cis), 3.31 (1H, m, trans+cis), 7.20–7.33 (5H, m, trans+cis). ^{13}C NMR: 11.1 (cis), 11.4 (trans), 26.8 (trans), 29.6 (cis), 35.9 (trans), 36.8 (trans), 39.2 (cis), 39.3 (trans), 39.8 (cis), 43.6 (cis), 46.3 (trans), 47.3 (trans), 48.7 (cis), 126.4 (trans), 126.8 (trans), 128.5 (trans), 144.3 (trans), 211.6 (trans). IR (neat): 1730. EIMS *m*/*z*: 202 (M^+).

(−)-(*R*)-**12c**: The ee was determined to be 88% by HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH=10:1, 0.5 mL/min, 254 nm, major 22 min and minor 25 min).

4.1.5. (−)-(*R*)-5-(Naphth-2-yl)cyclohexenone 12d (R^1= 2-naph) (entry 5). Chromatography (hexane/diethyl ether=20:1) gave a 87:13 trans/cis mixture of (−)-3-ethyl-5-(naphtha-2-yl)cyclohexanone **13** (R^1=2-naph, R^2=Et) (162 mg, 64% yield, 87% ee (trans)) as a colorless oil of $[\alpha]_D^{25}$ +5.90 (*c* 1.14, $CHCl_3$) and (−)-(*R*)-5-(naphth-2-yl)-cyclohexenone **12d** (71 mg, 33% yield, 95% ee) as solid of mp 107–109 °C and $[\alpha]_D^{25}$ −73.2 (*c* 0.56, $CHCl_3$).

(−)-**13** (R^1=2-Naph, R^2=Et): Major *trans*- and *cis*-**13** were determined to have 87% ee and 90% ee by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH=10:1, 0.5 mL/min, 254 nm, trans isomer: major 22 min and minor 24 min, cis isomer: major 31 min and minor 26 min). The ratio of trans/cis=87:13 was determined by the integration area of ^{1}H NMR signals of the trans Me (t) and the cis Me (t)). ^{1}H NMR: 0.89 (0.87H, t, *J*=7.3 Hz, trans), 0.96 (0.13H, t, *J*=7.3 Hz, cis), 1.38–1.51 (2H, m, trans+cis), 1.95–2.28 (4H, m, trans+cis), 2.57–2.78 (3H, m, trans+cis), 3.50 (1H, m, trans+cis), 7.37–7.83 (7H, m, trans+cis). ^{13}C NMR: 11.1 (cis), 11.4 (trans), 27.0 (trans), 29.9 (cis), 35.8 (trans), 36.8 (trans), 39.2 (cis), 39.5 (trans), 39.9 (cis), 43.8 (cis), 46.7 (trans), 47.1 (trans), 47.3 (cis), 48.7 (cis), 124.5 (cis), 125.0 (trans), 125.6 (trans), 126.1 (trans), 127.1 (trans), 127.5 (trans), 128.2 (trans), 132.2 (trans), 132.3 (cis), 133.4 (trans), 141.7 (trans), 143.1 (cis), 211.7 (trans). IR (neat): 1720. EIMS *m*/*z*: 252 (M^+). HRMS *m*/*z* calcd for $C_{18}H_{20}O$: 252.1514. Found: 212.1516.

(−)-(*R*)-**12d**: The ee was determined to be 95% by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH=3:1, 0.5 mL/min, 254 nm, major 25 min and minor 20 min). The absolute configuration was determined to be *R* by the specific rotation. ^{1}H NMR: 2.60–2.82 (m, 4H), 3.51 (m, 1H), 6.16 (d, *J*=10 Hz, 1H), 7.06 (m, 1H), 7.37 (d, *J*=8.6 Hz, 1H), 7.45–7.50 (m, 2H), 7.66 (s, 1H), 7.80–7.84 (m, 3H). ^{13}C NMR ($CDCl_3$): 33.5, 41.0, 44.8, 125.0, 125.2, 125.8, 126.3, 127.7, 127.8, 128.5, 129.8, 132.5, 133.5, 140.6, 149.4, 199.1. IR (Nujol): 1662. EIMS *m*/*z*: 222 (M^+). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.25; H, 6.49.

Acknowledgements

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