Synlett D.-C. Bai et al. Letter

Kinetic Resolution of Unsymmetrical Acyclic Allyl Carbonates Using Trimethylsilyl Cyanide via Palladium-Catalyzed Asymmetric Allylic Alkylation

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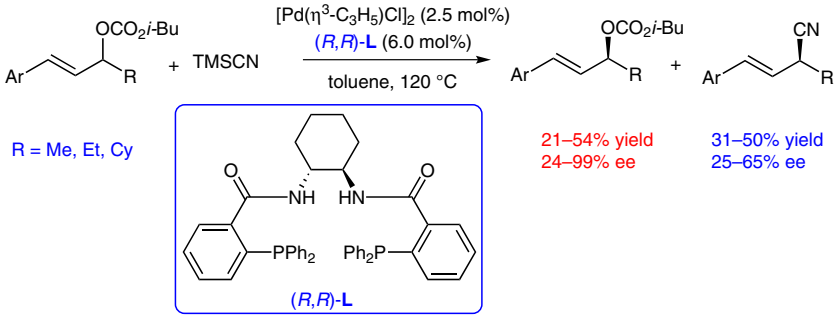
This paper is dedicated to Professor K. P. C. Vollhardt



Received: 09.03.2015
Accepted after revision: 07.05.2015
Published online: 01.06.2015
DOI: 10.1055/s-0034-1378709; Art ID: st-2015-b0166-l

Abstract The kinetic resolution of 1,3-disubstituted unsymmetrical allylic substrates with TMSCN as the nucleophile was realized via palladium-catalyzed asymmetric allylic alkylation, providing optically active allylic substrates and β,γ-unsaturated nitriles in good yield and enantioselectivity.

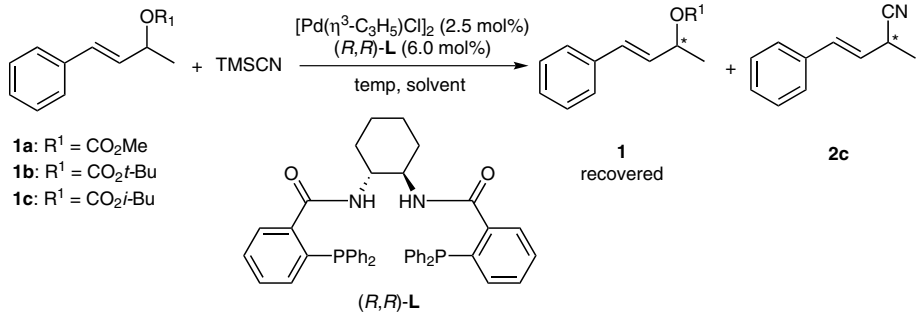
Key words kinetic resolution, palladium, asymmetric allylic alkylation, unsymmetrical acylic allyl carbonates, trimethylsilyl cyanide

The asymmetric catalytic cyanation reaction is a highly important enantioselective C–C bond-construction reaction employing cyanide as reagent. The resulting products containing a cyano group are easily transformed into other chiral building blocks such as natural and unnatural amino acids, β-lactams, and diamines.[2] Hence the development of an efficient asymmetric catalytic cyanation reaction has received wide attention of organic chemists for decades.[3] Although many asymmetric catalytic reactions such as Strecker reaction, Michael reactions, and ring-opening reaction of epoxides and aziridines have been realized using various cyanide sources,[4] the development of new asymmetric cyanation is still highly desirable.

Palladium-catalyzed asymmetric allylic alkylation is a powerful method in organic synthesis.[5a–d] A wide range of nucleophiles have been used in the reaction, affording many different kinds of optically active products.[5] The reaction has also been applied successively in the kinetic resolution of allyl substrates[6] as well as nucleophiles.[7] Although TMSCN has also been reported to be used in palladium-catalyzed allylic alkylation reaction,[8] few asymmetric versions of the reaction have appeared.[9] Herein, we present a kinetic resolution of 1,3-disubstituted unsymmetrical allylic substrates via a palladium-catalyzed asymmetric allylic cyanation with trimethylsilyl cyanide (TMSCN) as a nucleophile, which provides optical active allylic substrates and optical active β,γ-unsaturated nitriles in high yield and good enantioselectivity.

Initially, we examined the allylic substitution of allyl substrate **1a** utilizing TMSCN as the nucleophile in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (*R*,*R*)-DACH-phenyl Trost ligand (**L**) as catalyst. Delightfully, the allylation product **2c** was afforded in 24% yield with 44% enantiomeric excess while **1a** was recovered in 69% yield in 34% enantiomeric excess (Table 1, entry 1). Under the same reaction conditions, decreased reactivity was observed with allyl substrate **1b**, only 8% yield of **2c** being obtained (Table 1, entry 2) while the use of allyl substrate **1c** afforded product **2c** in 24% yield with 66% enantiomeric excess, and **1c** was recovered in 60% yield with 46% enantiomeric excess (Table 1, entry 3). The screen of solvents showed that toluene was the better choice over 1,2-dichloroethane (DCE), dioxane, dimethoxyethane (DME), and cycloheptane (Table 1, entries 3–7). The reactivity of **1c** increased when the reaction temperature was elevated. The reaction at 120 °C instead of 100 °C afforded **2c** in 45% yield with 55% enantiomeric excess, and **1c** was recovered in 51% yield with 88% enantiomeric excess in two hours (Table 1, entry 8 vs. entry 3). The effect of the reaction time and the equivalents of TMSCN on the reaction were also investigated, but no great changes were observed (Table 1, entries 9–11). The use of two other commercially available (*R*,*R*)-ANDEN-phenyl and (*R*,*R*)-DACH-naphthyl Trost ligands led to inferior results, while bisphosphine chiral ligand (*R*)-BINAP and chiral *P*,*N*-ligand (*S*)-*i*-Pr-PHOX demonstrated low catalytic activity (not shown in Table 1). The kinetic resolution of the compound **1c** with $K_4[Fe(CN)_6]\cdot 3H_2O$ or CuCN as nucleophile under the optimal reaction conditions was also performed, but the corre-

Table 1 Optimization of Reaction Parameters[a]



Entry	1	TMSCN (equiv)	Solvent	Time (h)	Temp (°C)	Yield of **1** (%)[b]/ee (%)[c]	Yield of **2c** (%)[b]/ee (%)[c]
1	**1a**	1.0	toluene	10	100	69/34	24/44
2	**1b**	1.0	toluene	10	100	85/8	8/70
3	**1c**	1.0	toluene	10	100	60/46	24/66
4	**1c**	1.5	DCE	12	100	31/0	2/–
5	**1c**	1.5	dioxane	12	100	61/20	1/–
6	**1c**	1.5	DME	12	100	49/39	22/51
7	**1c**	1.0	cycloheptane	12	100	66/20	13/64
8	**1c**	1.0	toluene	2	120	51/88	45/59
9	**1c**	1.0	toluene	1	120	65/43	35/65
10	**1c**	1.5	toluene	2	120	17/99	75/14
11	**1c**	0.7	toluene	7	120	51/51	28/70

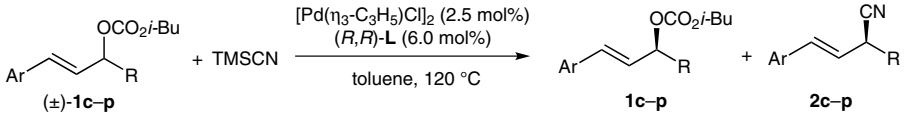
[a] Reaction conditions: **1**/[Pd(η3-C3H5)Cl]2/**L** = 100/2.5/6, **1** (0.2 mmol) in solvent (2.0 mL).
[b] Isolated yield.
[c] Determined by HPLC.

sponding product **2c** was not formed. Instead, (*E*)-buta-1,3-dien-1-ylbenzene derived from β-H elimination of compound **1c** was observed (not shown in Table 1).

On the basis of the optimal reaction conditions, the substrate scope of the kinetic resolution of 1,3-disubstituted unsymmetrical allylic substrates with TMSCN was investigated (Table 2).[10] Generally, the reactions provided optically active β,γ-unsaturated nitrile products **2** in 31–50% yields and 25–65% enantiomeric excess with recovered allyl starting materials **1** in 21–57% yields and 24–99% ee, *S* factors being between 2.3–10.7. Various substituents on the phenyl ring of allyl substrates **1** are tolerated, and the R group of allyl substrates **1** can be the methyl, ethyl, and cyclohexyl group. When unsymmetrical allyl substrates **1** have substituents at *para* and *meta* position of the phenyl ring, moderate *S* value was realized (Table 2, entries 2–8). When the substituents were located at *ortho* position of the phenyl ring of **1**, the *S* value was lower (Table 2, entries 9 and 13). If the phenyl group of **1** was changed to naphthyl, a lower *S* value was obtained (Table 2, entry 10 vs. entry 1). Replacing the methyl group of **1c** with the ethyl or cyclohexyl group had little effect on the kinetic resolution (Table 2, entries 11 and 14 vs. entry 1). The use of 1,3-diphenylallyl acetate as the substrate was tested, however, no reaction occurred in 12 hours, and the 1,3-diphenylallyl acetate was recovered in 96% yield. The reaction time affects the reaction results significantly. Long reaction time gave product **2** in high yield but with low enantiomeric excess accompanying the formation of β-H elimination product. The absolute configuration of the product **2c** was determined to be *S* by comparing its optical rotation and HPLC trace with that reported by RajanBabu.[11] The absolute configuration of the recovered **1c** was determined to be *S* by comparing the optical rotation of its corresponding allyl alcohol to that of literature reports.[12]

To further understand the mechanistic pathway of the reaction,[13] we carried out the reaction of *cis*-disubstituted substrate **3** with TMSCN under the standard reaction conditions of Table 2 (Scheme 1). *trans*-Product **4** was obtained in 61% yield. The results indicated the reaction proceeds through the attack of cyanide to the palladium instead of allyl moiety of the π-allylpalladium intermediate followed by stereoselective reductive elimination. These results are agreement with that reported by the Tsuji group.[8b]

Table 2 Substrate Scope for Kinetic Resolution[a,10]

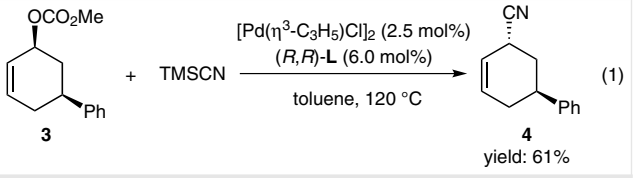


(±)-**1c–p** **1c–p** **2c–p**

1c: Ar = Ph, R = Me
1d: Ar = 4-MeC$_6$H$_4$, R = Me
1e: Ar = 4-BrC$_6$H$_4$, R = Me
1f: Ar = 4-ClC$_6$H$_4$, R = Me
1g: Ar = 4-F$_3$CC$_6$H$_4$, R = Me
1h: Ar = 3-MeC$_6$H$_4$, R = Me
1i: Ar = 3-MeOC$_6$H$_4$, R = Me
1j: Ar = 3-ClC$_6$H$_4$, R = Me
1k: Ar = 2-MeC$_6$H$_4$, R = Me
1l: Ar = 1-Np, R = Me
1m: Ar = Ph, R = Et
1n: Ar = 3-FC$_6$H$_4$, R = Et
1o: Ar = 2-MeOC$_6$H$_4$, R = Et
1p: Ar = Ph, R = Cy

Entry	Time (h)	Yield of recovered **1** (%)[b]/ee (%)[c]	Yield of **2** (%)[b]/ee (%)[c]	S[d]
1	2	**1c** 51/88	**2c** 45/59	10.7
2	3	**1d** 33/74	**2d** 33/52	6.7
3	2	**1e** 57/59	**2e** 35/65	8.4
4	2	**1f** 37/54	**2f** 42/47	4.6
5	3	**1g** 54/51	**2g** 35/55	5.6
6	3	**1h** 39/73	**2h** 50/57	7.7
7	3	**1i** 48/74	**2i** 42/60	8.6
8	3	**1j** 47/31	**2j** 44/52	4.2
9	3	**1k** 21/37	**2k** 50/25	2.3
10	3	**1l** 43/24	**2l** 31/42	3.1
11	1	**1m** 40/99	**2m** 48/39	10.1
12	3	**1n** 39/91	**2n** 44/50	8.8
13	3	**1o** 30/66	**2o** 42/43	4.7
14	2	**1p** 34/97	**2p** 39/43	9.3

[a] Reaction conditions: **1**/TMSCN/[Pd(η^3-C$_3$H$_5$)Cl]$_2$/**L** = 100:100:2.5:6, **1** (0.2 mmol) in toluene (2.0 mL).
[b] Isolated yield.
[c] Determined by HPLC.
[d] Calculated according to the method described by Kagan,[6a] $S = \ln[(1 - C/100)(1 - ee/100)]/\ln[(1 - C/100)(1 + ee/100)]$ ($C = ee/ee + ee'$; ee = enantiometric excess of recovered substrate; ee′ = enantiometric excess of product).



Scheme 1

In summary, we have realized the kinetic resolution of 1,3-disubstituted unsymmetrical allylic substrates with TMSCN as the nucleophile via palladium-catalyzed asymmetric allylic alkylation, which provides optically active allylic substrates and β,γ-unsaturated nitriles in good yield and enantioselectivity. Further investigations on the palladium-catalyzed asymmetric allylic cyanation are in progress in our laboratory.

Acknowledgment

Financial supported by the Major Basic Research Development Program (2011CB808706), National Natural Science Foundation of China (21272251, 21472214, 21421091), the NSFC and the Research Grants Council of Hong Kong Joint Research Scheme (21361162001), the Chinese Academy of Sciences, the Technology Commission of Shanghai Municipality, and the Croucher Foundation of Hong Kong.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378709.

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(1) These authors contributed equally.
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(9) Tsuji reported one example in ref. 8b.

(10) **General Procedure for Kinetic Resolution**

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.0 mg, 0.006 mmol) and ligand (*R,R*)-**L** (8.0 mg, 0.006 mmol) and toluene (1.0 mL) were added into a dry sealed tube (10 mL) and stirred at r.t. for 30 min. Compound **1** (0.2 mmol), TMSCN (30 μL, 0.2 mmol), and toluene (1.0 mL) were added to the sealed tube, then the reaction mixture was stirred at 120 °C immediately. After the reaction time show in Table 2, the reaction mixture was quenched by sat. Na_2CO_3 (0.5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was combined, dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil. Purification by chromatography on silica gel provided the desired product (eluting with PE–EtOAc = 10:1)

Compound **2c**: Yield 45%; 59% ee. $[\alpha]_D^{20}$ = 8.8 (*c* 0.44, $CHCl_3$).[4] ^{1}H NMR (400 MHz $CDCl_3$): δ = 7.26–7.39 (m, 5 H), 6.70–6.74 (d, *J* = 16.0 Hz, 1 H), 6.04–6.10 (dd, *J* = 16.0, 7.2 Hz, 1 H), 3.50 (m, 1 H), 1.50 (d,*J* = 7.2 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.7, 132.5, 128.7, 128.3, 126.5, 124.3, 120.9, 28.4, 19.1. MS (EI): *m/z* (rel. intensity) = 157 (66) [M$^+$], 158 (7), 156 (79), 142 (38), 129 (30), 115 (100), 102 (10), 91 (11), 89 (12), 77 (20), 63 (14), 51 (22). IR (film): ν = 2985 (w), 2242 (w), 1496 (w), 1449 (m), 1399 (m), 964 (m), 745 (s), 692 (s) cm^{-1}. HPLC (Chiralcel OD-H, hexane–2-PrOH = 95:5, 0.7 mL/min, 214 nm): t_R (major) = 12.14 min; t_R (minor) = 13.46 min. HRMS: *m/z* calcd for $C_{11}H_{10}N$ [M$^+$]: 157.0891; found: 157.0889.

Compound **1c**: Yield 51%; 88% ee. $[\alpha]_D^{20}$ = –75.8 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz $CDCl_3$): δ = 7.24–7.40 (m, 4 H), 6.63–6.67 (d, *J* = 16.0 Hz, 1 H), 6.18–6.24 (dd, *J* = 16.0, 7.2 Hz, 1 H), 5.36 (m, 1 H), 3.92 (d,*J* = 6.8 Hz, 2 H), 1.97 (m, 1 H), 1.46 (d, *J* = 5.6 Hz, 3 H), 0.95 (d, *J* = 7.2 Hz, 6 H). MS (EI): *m/z* (rel. intensity) = 248 (8.0) [M$^+$], 205 (7), 192 (1), 148 (39), 131 (100), 115 (43), 105 (31), 91 (59), 77 (16), 57 (46), 51 (8). HPLC (Chiralcel OD-H, hexane–2-PrOH = 99:1, 0.7 mL/min, 214 nm): t_R (major) = 7.18 min; t_R (minor) = 7.80 min.

Compound **2i**: Yield 42%; 60% ee. $[\alpha]_D^{20}$ = 8.4 (*c* 0.8, $CHCl_3$). ^{1}HNMR (400 MHz,$CDCl_3$): δ = 7.21–7.26 (m, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.90 (s, 1 H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.66–6.70 (d, *J* = 15.6 Hz, 1 H), 6.06 (dd, *J* = 16.0, 6.4 Hz, 1 H), 3.82 (m, 1 H), 3.51 (m, 1 H), 1.5 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8, 137.1, 132.4, 129.7, 124.6, 120.9, 119.1, 113.9, 111.9, 55.3, 28.4, 19.0. MS (EI): *m/z* (rel. intensity): 187 (100) [M$^+$], 186 (57), 172 (23), 156 (22), 144 (94), 128 (20), 115 (48), 102 (24), 91 (22), 77 (22), 63 (23), 51 (18). IR (film): ν = 2938 (m), 2836 (m), 2241 (m), 1599 (s), 1579 (s), 1453 (m), 1263 (m), 1041 (m), 964 (s), 775 (s), 688 (s) cm^{-1}. HPLC (Chiralpak PA-2, hexane–2-PrOH = 99:1, 1.0 mL/min, 214 nm): t_R (major) = 27.98 min; t_R (minor) = 31.74 min. HRMS: *m/z* calcd for $C_{12}H_{13}NO$ [M$^+$]: 187.0994; found: 187.0997.

Compound **1i**: Yield 48%; 74% ee. $[\alpha]_D^{20}$ = –60.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.21–7.26 (m, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.90 (s, 1 H), 6.83 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.66–6.70 (d, *J* = 16.0 Hz, 1 H), 6.06 (dd, *J* = 16.0, 6.4 Hz, 1 H), 5.36 (m, 1 H), 3.92 (d, *J* = 6.8 Hz, 1 H), 3.91 (s, 3 H), 1.97 (m, 1 H), 1.46 (d, *J* = 6.4 Hz, 2 H), 0.92 (d, *J* = 6.4 Hz, 9 H). MS (EI): *m/z* (rel. intensity): 278 (32) [M$^+$], 235 (2), 178 (33), 161 (75), 145 (42), 135 (100), 129 (18), 117 (26), 91 (34), 77 (14), 57 (51). HPLC (Chiralpak OJ-H, hexane–2-PrOH = 99.5:0.5, 0.7 mL/min, 214 nm): t_R (major) = 23.67 min; t_R (minor) = 29.92.

Compound **2p**: Yield 39%; 43% ee. $[\alpha]_D^{20}$ = 2.4 (*c* 0.85, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.25–7.40 (m, 5 H), 6.81–6.72 (d, *J* = 16.0 Hz, 1 H), 6.01 (dd, *J* = 16.0, 6.8 Hz, 1 H), 3.36 (m, 1 H), 1.67–1.82 (m, 6 H), 1.19–1.26 (m, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.8, 133.9, 128.7, 128.1, 126.5, 122.1, 119.4, 41.1, 40.8, 31.0, 29.6, 26.0, 25.8. MS (EI): *m/z* (rel. intensity): 225 (8) [M$^+$], 143 (100), 128 (2), 115 (25), 102 (2), 91 (4), 83 (13), 65 (3), 55 (46). IR (film): ν = 2922 (m), 2854 (m), 2233 (w), 1449 (m), 974

(m), 746 (s), 691 (m) cm^{-1}. HPLC (Chiralpak AD-H, hexane–2-PrOH = 99:1, 0.7 mL/min, 214 nm): t_R (minor) = 20.65 min; t_R (major) = 30.04 min. HRMS: *m/z* calcd for $C_{16}H_{19}N$ [M^+]: 225.1514; found: 225.1517.

Compound **1p**: Yield 34%; 97% ee. $[\alpha]_D^{20}$ = –29.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.40 (m, 5 H), 6.65 (d, *J* = 16.0 Hz, 1 H), 6.15 (dd, *J* = 16.0, 8.0 Hz, 1 H), 5.03 (m, 1 H), 3.92 (d, *J* = 6.8 Hz, 1 H), 2.02 (m, 1 H), 1.88 (m, 1 H), 1.60–1.82 (m, 5 H), 1.01–1.20 (m, 5 H), 0.92 (dd, *J* = 6.8, 2.0 Hz, 6 H). MS (EI): *m/z* (rel. intensity): 316 (3) [M^+], 216 (12), 199 (14), 169 (3), 156 (6), 141 (11), 133 (100), 117 (35), 91 (25), 83 (16), 57 (41), 55 (32). HPLC (Chiralpak OD-H, hexane–2-PrOH = 99.5:0.5, 0.7 mL/min, 214 nm): t_R (minor) = 20.65 min; t_R (major) = 30.04 min.

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