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Palladium(0)-catalyzed cascade one-pot synthesis of isoxazolidines

Krishna Gopal Dongol* and Boon Ying Tay

Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore

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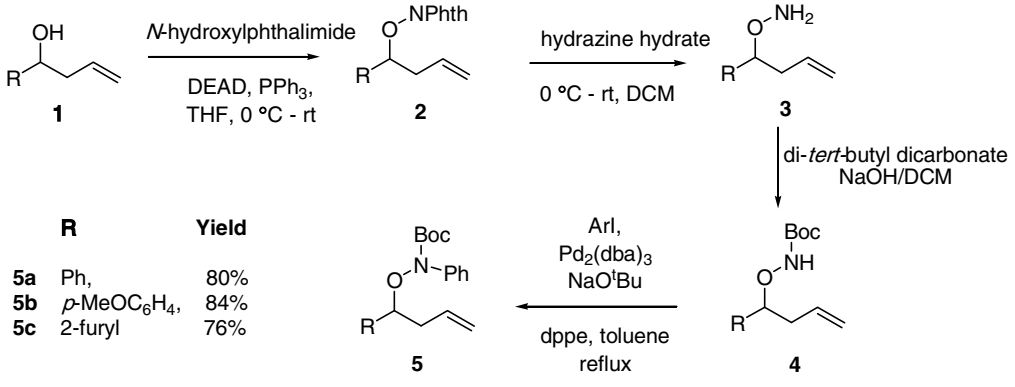
Abstract—A highly diastereoselective cascade reaction protocol has been developed for the synthesis of isoxazolidine derivatives utilizing aryl halides, *O*-homoallyl hydroxylamine and palladium(0) in a one-pot reaction.

The use of palladium-catalyzed cascade reactions in the synthesis of heterocyclic compounds of biological interest continues to receive widespread attention.[1] Recently, heterocyclic rings such as tetrahydrofurans[2] and pyrrolidines[3] were synthesized with good to excellent stereoselectivity by the cascade method, employing a suitable Pd^0 catalyst and the requisite aryl halides and alkenes. There are no reports, however, describing the use of a palladium-mediated cascade sequence for substrates containing an alkene with tethered nitrogen, in which the construction of both C–N and C–C bonds could conceivably be achieved in a one-pot event.[4] We decided to investigate this area using functionalized *O*-homoallyl hydroxylamines such as **4** where the N–O bond would serve as a tether in facilitating an intramolecular process. This chemistry could potentially offer a convenient entry to 3,5-disubstituted isoxazolidines, which serve as valuable synthetic building blocks for the construction of bioactive natural products[5,6] and as precursors for β-amino ketones.[7]

To examine this hypothesis, a series of *N*-Boc protected hydroxylamines **4** were prepared from the corresponding alcohols **1**[8] via the Mitsunobu protocol.[9] *O*-Homoallylic alcohol **1** was treated with *N*-hydroxyphthalimide, triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) in THF furnishing hydroxylamine ether **2**. The phthaloyl moiety (Phth) was then cleaved by treatment with hydrazine hydrate at 0 °C to room temperature, leading to *O*-homoallyl hydroxylamine **3**.[10] Protection



	R	Yield
5a	Ph,	80%
5b	*p*-$MeOC_6H_4$,	84%
5c	2-furyl	76%

Scheme 1.

Keywords: Cascade reaction; Palladium(0); Isoxazolidine; *O*-Homoallyl hydroxylamine.
* Corresponding author. Tel.: +65 6796 3917; fax: +65 6316 6184; e-mail: Krishna_dongol@ices.a-star.edu.sg

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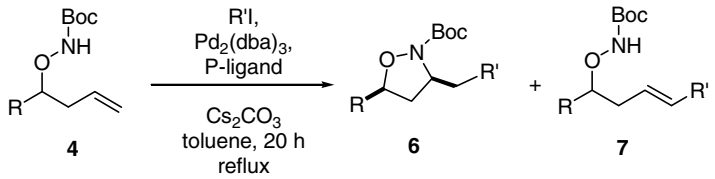

a R = Ph R' = Ph **c** R = 2-furyl R' = Ph
b R = *p*-MeOC$_6$H$_4$ R' = Ph **d** R = Me R' = Ph

Scheme 2. Substituent effects.

Table 1. Substituent effects

Entry	R	R′	GC yield[a] (%)		Cis/trans[b] ratio of **6**
			6	**7**	
a	Ph	Ph	52	48	6:1
b	*p*-MeOC$_6$H$_4$	Ph	64	36	10:1
c	2-Furyl	Ph	74	26	3:1
d	CH$_3$	Ph	11	89	—
e	*p*-MeOC$_6$H$_4$	*p*-MeOC$_6$H$_4$	8	92	—
f	*p*-MeOC$_6$H$_4$	*p*-O$_2$NC$_6$H$_4$	61	39	2:1

[a] The ratio (%) was based on gas chromatographic analysis.
[b] The cis/trans ratio of **6** was based on ^{1}H NMR analysis. In the case of entries 4 and 5, we are unable to isolate pure cyclized compounds **6**.

of **3** as its *N*-Boc carbamate then completed the synthesis of **4**, setting the stage for the investigation of palladium-mediated isoxazolidine formation (Scheme 1).

In the initial studies, an attempted Pd$_2$(dba)$_3$-catalyzed reaction between *N*-Boc hydroxylamine ether **4** and iodobenzene in the presence of NaO^{t}Bu failed to provide the desired isoxazolidine **6**. Instead, amide **5** resulting from direct amination of iodobenzene with **4** was observed as the sole product. A possible explanation is that the strong base, NaO^{t}Bu, abstracts the amide *N*-hydrogen and thus facilitates N-arylation.[11] To circumvent the formation of this undesired product, Cs$_2$CO$_3$ was employed as an alternative,[12] and under this modified procedure, isoxazolidine **6b**, for example, was obtained in 60% isolated yield, together with the Heck coupling adduct **7b**, in 21% yield as shown in Scheme 2.

To determine the scope of this reaction, a series of reactions were carried out with a variety of R-substituted *N*-Boc-hydroxylamine ethers (Ph, *p*-MeOC$_6$H$_4$, Me, 2-furyl) and aryl iodides (R′ = *p*-MeOC$_6$H$_4$, Ph, *p*-O$_2$NC$_6$H$_4$).

The product distribution is summarized in Table 1 in reference to Scheme 2.

It was evident that the substituents R and R′ influenced the ratio of products obtained to some degree. In general, when R was electron donating in nature, the cyclic product **6** was favoured, while if R′ was an electron donating group the Heck type product **7** was preferred.

In order to suppress the formation of the undesired Heck product **7**, the effect of catalyst loading was examined. Unfortunately, no improvement in product distribution was observed when the catalyst loading was varied from 1 to 20 mol %.

However, the choice of the phosphine ligand does play a role in the observed product ratio. In the presence of P(Cy)$_3$ or P(*o*-Tol)$_3$, an approximately 3:1 ratio in favour of isoxazolidine **6b** was observed. In contrast, a reversed product distribution favouring the Heck adduct **7b** was found when P(^{t}Bu)$_3$ was employed. These results are summarized in Table 2 in reference to the reaction in Scheme 2. The best result for the isoxazolidine **6b** over Heck type product **7b** was obtained when 1 mol% P(*o*-Tol)$_3$ was used.

A mechanistic rationale for the observed products is summarized in Figure 1. The first part of the catalytic cycle is believed to proceed through the standard Heck pathway, where an initial oxidative insertion of Pd^0 into the aryl halide R′X is followed by *syn* carbopalladation across the terminal olefin to afford intermediate **9**.

The relative rates of the subsequent β-hydride elimination versus nitrogen coordination in intermediate **9**

Table 2. Ligand effects

Entry	P-ligands	GC yield[a] (%)	
		6b	**7b**
1	dppe	52	48
2	P(Cy)$_3$	72	28
3	P(*o*-Tol)$_3$	79	21
4	P(^{t}Bu)$_3$	30	70

R = *p*-MeOC$_6$H$_4$ and R′ = Ph.
[a] The product ratio and conversion was based on gas chromatographic (GC) analysis based on 100% conversion.

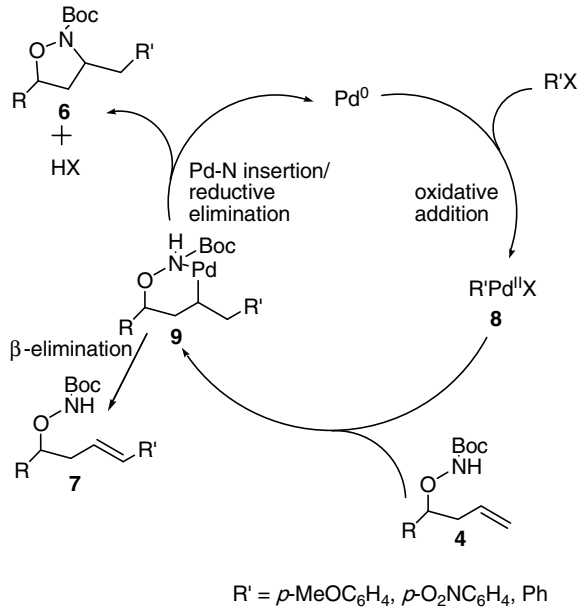

Figure 1. Proposed catalytic cycle leading to **6** and **7**.

determine the observed product distribution. Moreover, the carbonyl oxygen of the *N*-Boc group may also offer additional stabilization through its participation via intramolecular chelation, thereby stabilizing intermediate **9** and suppressing β-hydride elimination. The presence of electron-donating phosphine ligands on the Pd will accelerate C–N bond formation by accelerating the reductive elimination,[13] hence, the use of $P(Cy)_3$ or $P(o\text{-Tol})_3$ favours product **6** over β-hydride elimination product **7**.

A 10:1 the cis/trans ratio[14] of the 3,5-substituents in isoxazolidine **6b** was established by integration of the ^1H NMR spectrum. The stereochemistry of the major isomer of **6b** was determined by NOE and NOESY[15] studies, and is believed to arise from transition state **A** as depicted in Figure 2.

A rationale for the cis selectivity can be gained by examining the reactive conformations (Fig. 2). Chelation of Pd^{II} with the nitrogen lone pair is favoured in conformation **A** as compared to conformation **B**, leading to the formation of the cis-diastereomer as the major product.

In summary, a novel, cascade sequence leading to the formation of isoxazolidines **6** has been developed. A systematic study of substituent effects and the application of this route to natural product synthesis is currently underway.

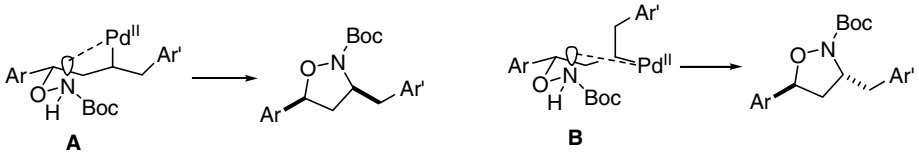

Figure 2. Conformations leading to the cis selectivity.

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12. Representative experimental procedure: A 50 mL Schlenk flask was charged with 3.1 mg $Pd_2(dba)_3$ (1 mol %, 0.003 mmol), 145 mg Cs_2CO_3 (1.3 equiv, 0.44 mmol), 1.4 mg (1 mol %, 0.0034 mmol) 1,2-bis(diphenylphosphino)ethane (dppe) using a glove box. The Schlenk flask was then evacuated and back filled with argon three times. Toluene (5 mL) and 100 mg of *N*-Boc hydroxylamine **4b** (0.34 mmol) and 90 mg (1.3 equiv, 0.44 mmol) iodobenzene were added to the flask under argon, then the reaction mixture was refluxed for 20 h. The mixture was filtered through a pad of silica gel and washed with ethyl acetate. Evaporation of the solvent provided the crude product which was further purified by flash column

chromatography which afforded isoxazolidine **6b** (73 mg, 0.2 mmol, 60%) as a colourless oil and Heck product **7b** (27 mg, 0.07 mmol, 21%) as a colourless oil.

Compound **6b**: IR (neat): *v* 3314, 2977, 2934, 1732, 1683, 1615, 1515, 1440, 1367, 1305, 1250, 1173, 1035, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (m, 7H), 6.80 (d, 2H, *J* 8.4 Hz) 4.74 (dd, 1H, *J* 6.4, 3.6 Hz), 4.44 (m, 1H), 3.73 (s, 3H, OCH_3), 3.11 (dd, 1H, *J* 6.4, 7.2 Hz), 2.77 (dd, 1H, *J* 7.6, 6.0 Hz), 2.54 (m, 1H), 1.94 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 159.7, 156.5, 137.1, 128.5, 128.1, 127.5, 127.1, 125.4, 112.9, 81.8, 80.7, 60.9, 54.3, 41.5, 41.2, 27.2. EIMS: *m*/*z* (70 eV) 369 (2), 252 (11), 236 (39), 205 (15), 178 (78), 162 (37), 135 (100), 119 (80), 91 (79), 57 (47), 41 (61). HRMS $C_{22}H_{27}NO_4$: calcd 369.1943, found 369.1943.

Compound **7b**: IR (neat): *v* 3307, 2978, 2933, 1760, 1612, 1367, 1248, 1172, 1033, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.13 (m, 7H), 6.84 (br s, 1H, NH) 6.83 (d, 2H, *J* 8.2 Hz), 6.37 (d, 1H, *J* 15.8 Hz), 6.05 (dt, 1H, *J* 15.8, 7.2 Hz), 4.74 (t, 1H, *J* 6.9 Hz), 3.70 (s, 3H, OCH_3), 2.83 (m, 1H), 2.59 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 159.6, 156.5, 137.4, 132.5, 131.6, 128.7, 128.4, 127.1, 126.1, 125.4, 113.9, 86.7, 81.6, 55.3, 38.6, 28.2. EI MS: *m*/*z* (70 eV) 369 (2), 279 (2), 252 (13), 236 (89), 205 (57), 178 (63), 152 (42), 135 (100, M^{+1}), 121 (77), 91 (67), 56 (33), 41 (57). HRMS: $C_{22}H_{27}NO_4$: calcd 369.1943, found 369.1947.

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14. The cis/trans ratio of isoxazolidine **6b** was determined as 10:1 from ^1H NMR integration of the OMe resonance at $\delta = 3.73$ ppm for major isomer and $\delta = 3.79$ ppm for minor isomer.

15. The NOESY experimental data showed a distinct correlation between the protons H-3 and H-5.