Facile Synthesis of Isoindolin-1-ones *via* Palladium-Catalyzed Carbonylative Cyclization of 2-Bromobenzaldehyde with Primary Amines

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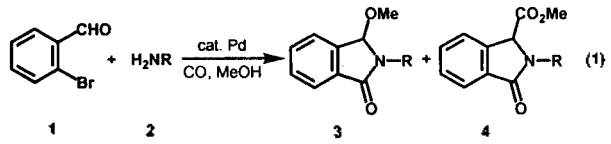
Transition metal-catalyzed carbonylative heterocyclization has been a useful synthetic tool for the formation of a variety of heterocyclic compounds such as lactams, lactons and imides.[1] Thus, the carbonylative heterocyclization has been effectively applied to the synthesis of isoindolinones *via* the cobalt-catalyzed carbonylative cyclization of Schiff's bases[2] and *o*-bromobenzylamines under sunlamp-irradiated phase transfer catalyst (PTC) conditions[3] as well as the palladium-catalyzed carbonylative cyclization of *N*-benzyl-*o*-bromobenzylamine,[4] *o*-bromobenzylbromide with primary amines,[5] and 2-(2-bromophenyl)-2-oxazolines.[6] In addition, Heck *et al.* reported on the formation of 3-substituted isoindolin-1-ones through carbonylation of *o*-palladated benzaldimines and tertiary benzylic amines.[7] However, this reaction has a drawback since it requires a stoichiometric amount of expensive palladium salt. We here report a facile synthesis of 3-methoxy- and 3-carbomethoxyisoindolin-1-ones *via* palladium-catalyzed carbonylative cyclization of 2-bromobenzaldehyde with primary amines.



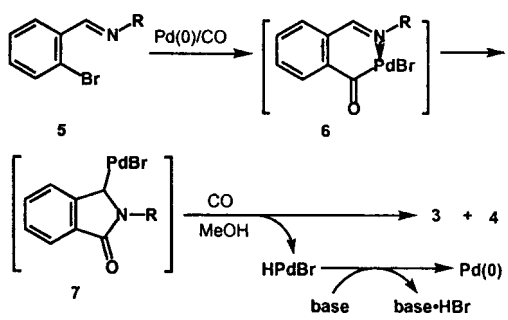
a: R = CH_2Ph
b: R = $CH_2(CH_2)_2CH_3$
c: R = Ph
d: R = 4-MeC_6H_4
e: R = 4-ClC_6H_4
f: R = 4-$MeOC_6H_4$

Treatment of 2-bromobenzaldehyde (**1**) with an equimolar amount of benzylamine (**2a**) in methanol under carbon monoxide (13 atm) in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (1.5 mol%) and sodium acetate (2.5 mol equiv) at 100 ℃ for 5 h afforded N-benzyl-3-methoxyisoindolin-1-one (**3a**) and *N*-benzyl-3-carbomethoxyisoindolin-1-one (**4a**) in 58 % yield (**3a**/**4a** = 69/31) (eq. 1).[8] Higher pressure of CO showed no considerable influence on both the yield of products and the ratio of **3a**/**4a**, whereas the ratio increased with the decrease of the pressure of CO (5 atm) for a longer reaction time (52% yield, **3a**/**4a** = 87/13). Among bases examined, sodium acetate revealed to be the most effective; using other bases such as K_2CO_3, $NaHCO_3$, and Et_3N in place of sodium acetate did not afford desirable yields of both products (2-23% yields). However, although the exact role of Et_3N for the reverse selectivity is obscure and remains unexplained in present stage, it is interesting when compared to other bases examined. From other easily available primary amines, except for **2f** which favored the formation of the more carbonylated product **4f**, both the corresponding isoindolin-1-ones were also formed in moderate yields with the selectivity for **3**. Typical results are summarized in Table 1.

Table 1. Palladium-Catalyzed Synthesis of 3-Substituted Isoindolin-1-ones

Amine	Base	CO (atm)	Time (h)	Isolated yield (%)	Ratio (3/4)
2a	NaOAc	13	5	58	69/31
2a	NaOAc	23	5	51	66/34
2a	NaOAc	5	20	52	87/13
2a	K_2CO_3	13	5	2[a]	100/0
2a	$NaHCO_3$	13	5	18[a]	83/17
2a	Et_3N	13	5	23[a]	35/65
2b	NaOAc	13	5	45	56/44
2c	NaOAc	13	5	40	63/37
2d	NaOAc	13	5	42	67/33
2e	NaOAc	13	15	52	67/33
2f	NaOAc	13	5	52	37/63

[a] Determined by GLC.



Scheme 1.

The reaction seems to proceed as shown in Scheme 1. Thus, oxidative addition of carbon-bromide bond of Schiff's base **5**, initially formed *in situ* by the reaction between **1** and **2**, to palladium(0) produces an arylpalladium(II) compound, where CO coordination to Pd and then aryl migration from Pd to carbon of CO occurs to give an acylpalladium(II) intermediate **6**. This is followed by intramolecular addition of the acylpalladium to the carbon-nitrogen double bond (*acylpalladation*[9]) to give the alkylpalladium species **7**. The intermediate reacts with methanol and CO/methanol to give **3** and **4**, respectively. A similar catalytic cycle has already been proposed in the carbonylative cyclization reactions.[10]

Studies on the selectivity arising from the kind of bases and the electronic nature of nucleophilic amines of this reaction and the application of other nucleophiles for synthetic utility are in progress.

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8. Spectroscopic data are as follows. **3a**: colorless oil; IR (neat) 1707 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3H), 4.20 (d, J=14.4 Hz, 1H), 5.18 (d, J=14.4 Hz, 1H), 5.71 (s, 1H), 7.26-7.39 (m, 5H), 7.46-7.57 (m, 3H), 7.86-7.88 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.1, 49.4, 85.6, 123.5, 123.7, 127.6, 128.6, 128.7, 130.0, 132.1, 133.0, 136.8, 140.4, 167.5; MS m/z (relative intensity) 253 (M^+, 29), 222 (23), 194 (6), 133 (36), 91 (100), 77 (12). **4a**: colorless oil; IR (neat) 1734 (C=O), 1697 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.29 (d, J=14.4 Hz, 1H), 4.93 (s, 1H), 5.47 (d, J=14.4 Hz, 1H), 7.24-7.36 (m, 5H), 7.51-7.57 (m, 3H), 7.88-7.91 (m, 1H); MS m/z (relative intensity) 281 (M^+, 18), 222 (68), 133 (6), 91 (100).
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Catalytic Enantioselctive Reactions. Part 10. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Oxazaborolidines

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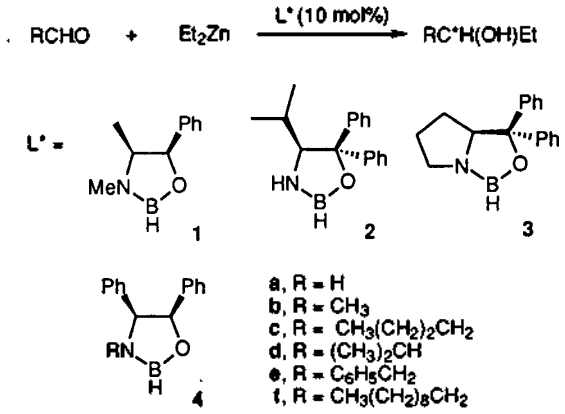
Catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention for the asymmetric synthesis of optically active secondary alcohols.[1] Accordingly, a wide range of catalysts for such reaction has been extensively developed.[1a] Among them, most of highly effective chiral catalysts for the reaction are both natural and synthetic β or γ-amino alcohols[2] (or thiols).[3] In 1989, Brown *et al.* repoted that a chiral oxazaborolidine, (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine (**1**), prepared from (1*R*,2*S*)-ephedrine with borane dimethyl sulfide provided 95% *ee* for the ethylation of benzaldehyde (Scheme 1). This value is superior to 66% ee obtained by the ephedrine itself.[4] They explained that the higher enantioselectivity of **1** might be attributable to more rigid structure of the catalyst by the formation of shorter B-O and B-N bonds than those of zinc metal. Recently, a number of chiral oxazaborolidines used as chiral catalysts for asymmetric borane reduction of ketones has been reported.[5] However, to the best of our knowledge, the use of other chiral oxazaborolidines with the exception of **1** for the ethylation to aldehydes has not been reported in literatures. Therefore, it appeared desirable to examine the catalytic asymmetric ethylation using other chiral oxazaborolidines. We chose first geminal diphenyl substituted oxazaborolidines, such as Itsuno's reagent (**2**)[6] and Corey's reagent (**3**),[7] which provided high enantioselctivities for borane reduction of ketones and tested the asymmetric ethylation using these reagents for benzaldehyde chosen as a model substrate. Thus, the reaction was carried out with addition of 2 equiv of diethylzinc to benzaldehyde in the presence of 10 mol% of **2** or **3** in toluene at room temperature (*ca.* 25 ℃). Unfortunately, the reaction provided the product alcohol of 62% *ee* and 16% *ee*, respectively. During this study, we found that an *erythro* diphenyl oxazaborolidine, (4*S*,5*R*)-3-isopropyl-4,5-diphenyl-1,3,2-oxazaborolidine (**4d**) generated from (1*R*,2*S*)-2-*N*-monoisopropylamino-1,2-diphenylaminoethanol (**5d**)[8] and borane dimethyl sulfide by literature procedure,[9] afforded 80% ee for benzaldehyde under the same reaction conditions. In this reaction, we observed that decrease of steric size of R in **4** diminished asymmetric inductions dramatically (entries 1, 2 and 3 in Table 1). At 0 ℃, the reaction proceeded much slowly with somewhat lower enantioselectivity (entry 5). Using **4d** as a chiral catalyst, substituted aryl aldehydes, such as *o*-, *p*-tolualdehyde and *p*-chlorobenzaldehyde, were alkylated to the corresponding alcohols with 69-77% *ee* (entries 1, 2, and 4 in Table 2). However, only low enantiomeric excesses (21-47% *ee*) were achieved for an unhindered aliphatic aldehyde, heptanal (entries 5-8). Addition to relatively hindered aliphatic aldehyde, such as 2,2-dimethylpropanal



Scheme 1.