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Mild Conditions for the Synthesis of Functionalized Pyrrolidines via Pd-Catalyzed Carboamination Reactions

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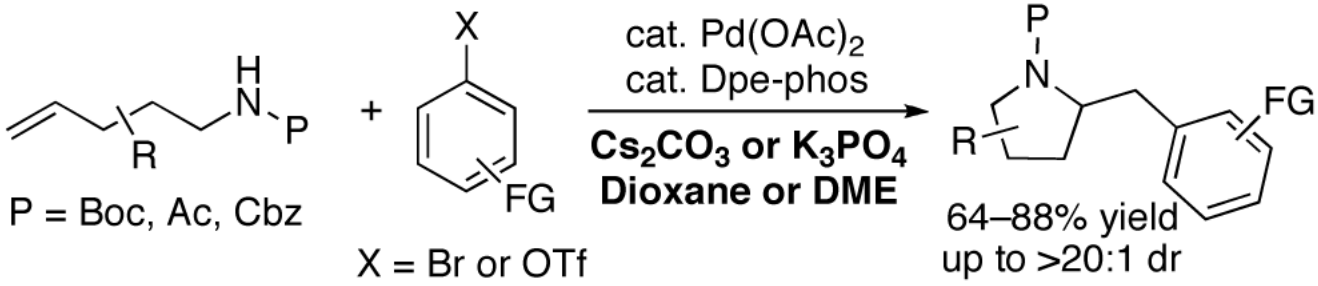
Abstract



The palladium-catalyzed carboamination of *N*-protected γ-aminoalkenes with aryl bromides and -triflates has been achieved under new, mild reaction conditions using the weak base Cs_2CO_3 in dioxane solvent. These reactions tolerate a wide variety of functional groups, including enolizable ketones, nitro groups, methyl esters, and acetates, which are not compatible with previously described conditions.

The development of synthetic methods for the construction of substituted pyrrolidines has been of longstanding importance in organic chemistry due to the prevalence of this moiety in biologically active molecules and natural products.[1] Over the past several years, the palladium-catalyzed carboamination of γ-aminoalkenes with aryl bromides has emerged as an efficient and stereoselective method for the construction of substituted pyrrolidine derivatives.[2,3] These transformations effect tandem cyclization and coupling in a process that generates a C—N bond, a C—C bond, and up to two stereocenters in one step. For example, treatment of Boc-protected amine **1**with 4-bromoanisole in the presence of NaO*t*Bu and catalytic amounts of $Pd_2(dba)_3$ and dppb afforded pyrrolidine **2** in 60% yield with >20:1 dr (eq 1).[2c]

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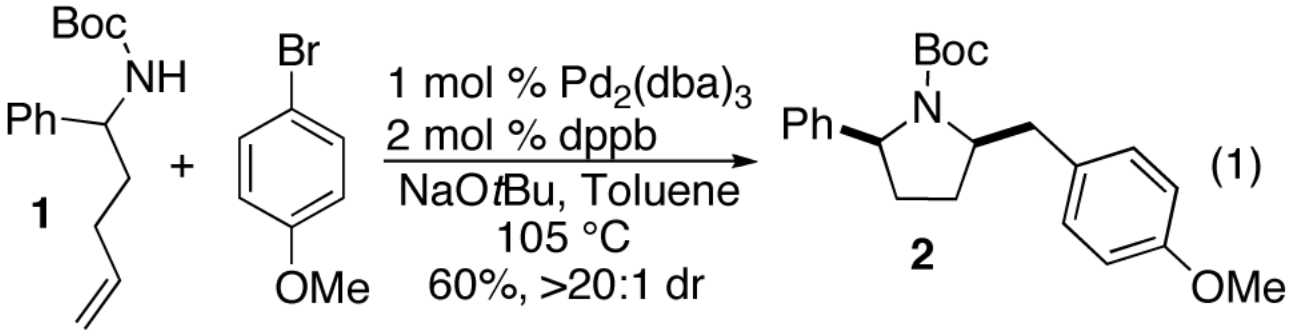
Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds reported in the text (65 pages). This material is available free of charge via the Internet at http://pubs.acs.org.



Despite the synthetic utility of these transformations, the reactions are typically conducted in the presence of the strong base NaO*t*Bu, which limits the scope of this method. For example, the use of NaO*t*Bu restricts the functional group tolerance of these reactions, and transformations of aryl triflate electrophiles, which decompose in the presence of strong base, have not been reported. Additionally, Cbz protecting groups, which are frequently employed in the synthesis of complex alkaloids, are incompatible with the strongly basic conditions. In this Letter we describe the development of new conditions that replace NaO*t*Bu with weaker bases (Cs_2CO_3 or K_3PO_4), which significantly expands the scope of the carboamination method.

In our preliminary studies on palladium-catalyzed carboamination reactions of γ-(*N*-Boc-amino)- or γ-(*N*-acylamino)alkenes, our attempts to conduct the transformations using bases other than NaO*t*Bu were met with limited success.[2c] For example, the $Pd_2(dba)_3$/Dpe-phos[4] catalyzed carboamination of **3** with 4-bromo-*tert*-butylbenzene afforded **4** in 81% yield when the reaction was conducted in toluene solvent with NaO*t*Bu as base (Table 1, entry 1). However, use of Cs_2CO_3 in place of NaO*t*Bu provided only a 38% isolated yield of **4**, and led to the formation of large amounts of side products (entry 2).[5,6].

To improve the yields obtained in Pd-catalyzed carboamination reactions that employ mild bases, the effect of palladium source and solvent were systematically examined; the key results of these studies are summarized in Table 1. After some experimentation, it was discovered that use of $Pd(OAc)_2$ in place of $Pd_2(dba)_3$ leads to significantly improved yields of **4** (63%, entry 3), and replacement of toluene with dioxane as solvent provides optimal results (82%, entry 4).[7,8]

As shown in Table 2, the new reaction conditions described above are effective for the transformation of a number of different substrate combinations. A variety of functional groups are tolerated under these mild conditions, including aldehydes (entry 3), enolizable ketones (entry 4), nitro groups (entries 6 and 11), methyl esters (entries 8 and 14), and alkyl acetates (entry 9). In addition, the carboamination reactions of electron-rich (entry 10), electron-neutral (entries 1, 2, 5, 7, and 13), and heterocyclic (entry 12) aryl bromides proceed with good chemical yields. The mild conditions also are effective for stereoselective reactions, and provide selectivities that are comparable to those observed in reactions that use NaO*t*Bu as base. For example, transformations of starting materials **1** and **9**, which bear a substituent adjacent to the nitrogen atom, provide *cis*-2,5-disubstituted products **20** and **21** with excellent (>20:1) diastereoselectivity (entries 11—12). Similarly, substrates **7** and **8**, which are substituted at the allylic position, are transformed to *trans*-2,3-disubstituted products **18** and **19** with good stereocontrol (12 to 15:1).

In addition to providing increased tolerance of base-sensitive functional groups, the new reaction conditions also allow the efficient carboamination of substrates bearing Cbz-protecting groups. For example, the Pd-catalyzed coupling of **6** with 2-bromonaphthalene using Cs_2CO_3 as base provided the desired product **16** in 88% isolated yield (entry 7). In contrast, cleavage of the Cbz-group from the substrate was problematic when reactions were conducted with NaO*t*Bu as base; these conditions provided only a 17% yield of **16**.

More complex γ-aminoalkene substrates are also efficiently transformed using the new reaction conditions. As shown in Table 2 (entries 13—14), Pd-catalyzed reactions of **10** with bromobenzene or methyl-4-bromobenzoate proceeded smoothly to provide **22** and **23** with excellent stereoselectivity. Trisubstituted pyrrolidine **22** has been previously employed as an intermediate in the synthesis of the natural product (+)-preussin.[2g,9]

The high degree of functional group tolerance of this method also allows straightforward access to 1-substituted tetrahydropyrroloisoquinolin-5-ones. As shown in Scheme 1, the Pd-catalyzed reaction of **8** with methyl-2-bromobenzoate afforded pyrrolidine **24** in 73% yield with 14:1 dr. Treatment of this product with trifluoroacetic acid followed by an alkaline workup gave **25** in 95% yield.

The main limitations of these new reaction conditions involve transformations of sterically encumbered substrate combinations.[10] For example, attempts to convert substrates bearing internal alkenes to pyrrolidines were unsuccessful under these conditions. In addition, the reaction of methyl 2-bromobenzoate with **1**, which bears a substituent on C-1 (adjacent to the nitrogen atom), was not effective. However, as noted above, this *o*-substituted aryl bromide was effectively coupled with the less hindered carbamate **8**(Scheme 1).

In addition to greatly expanding the scope of Pd-catalyzed carboamination reactions involving aryl bromide substrates, the use of mildly basic reaction conditions also allows the first Pd-catalyzed carboamination reactions with aryl triflates. Our preliminary efforts to conduct these transformations with the strong base NaO*t*Bu were unsuccessful due to competing cleavage of the trifluoromethanesulfonate ester, which resulted in conversion of the aryl triflate to the corresponding phenol. For example, treatment of **3** with 4-formylphenyl triflate in the presence of catalytic $Pd(OAc)_2$/Dpe-phos and stoichiometric NaO*t*Bu failed to generate the desired pyrrolidine product **12**. However, subsequent experiments demonstrated that use of K_3PO_4 as base provides the desired pyrrolidine **12** in 67% yield (Table 3, entry 1). These conditions are effective with both Boc- and Cbz-protected substrates, and diastereoselectivities are similar to those obtained in related reactions with aryl bromide electrophiles (entries 3-4).

In conclusion, we have developed new conditions for palladium-catalyzed carboamination reactions of *N*-protected γ-aminoalkenes with aryl bromides and triflates. These conditions, which use Cs_2CO_3 or K_3PO_4 in place of the strong base NaO*t*Bu, tolerate the presence of a broad array of functional groups, and significantly expand the scope of this method. Applications of these new conditions to the synthesis of complex pyrrolidine alkaloids are currently being pursued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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4. Dpe-phos = bis(2-diphenylphosphinophenyl)ether.

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6. Lower yields were obtained with other weak bases including K_2CO_3 and Et_3N.

7. In some cases use of DME as solvent provided comparable results to those obtained with dioxane (Table 2, entries 3, 4, 6, and 8.)

8 a). The differences in reactivity between $Pd_2(dba)_3$ and $Pd(OAc)_2$ are not fully understood, but may result from coordination of dba (dibenzylideneacetone) to the metal at key stages in the catalytic cycle, or through the formation of dba-ligated complexes that lie outside of the catalytic cycle. Dba has previously been demonstrated to have a large impact on the rates of Pd-catalyzed or mediated process. For lead references, see: Shekhar S, Ryberg P, Hartwig JF, Mathew JS, Blackmond DG, Strieter ER, Buchwald SL. J. Am. Chem. Soc 2006;128:3584–3591.3591 [PubMed: 16536531] b) Amatore C, Broeker G, Jutand A, Khalil F. J. Am. Chem. Soc 1997;119:5176–5185.5185

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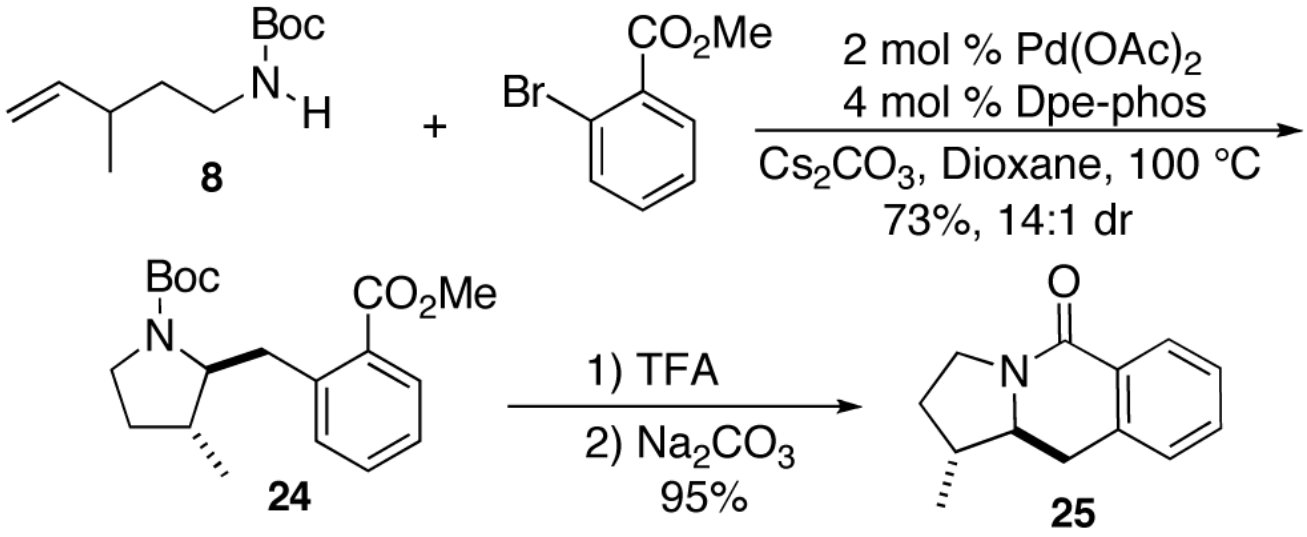
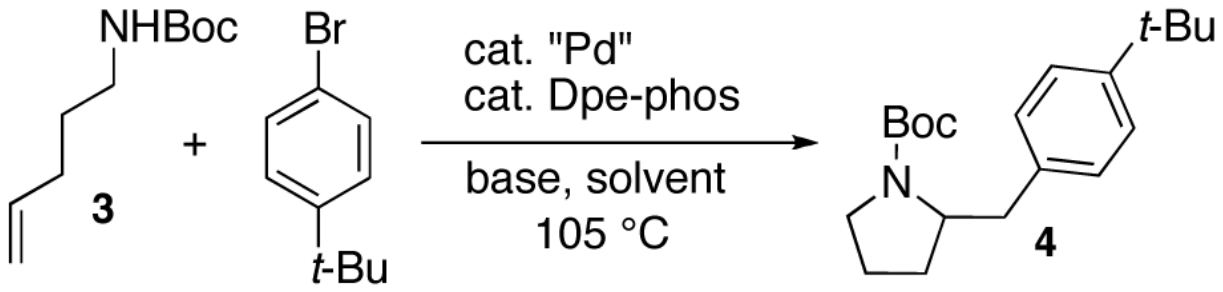
10. These conditions were also less effective for carboamination reactions of γ-(*N*-arylamino)alkenes; the desired *N*-arylpyrrolidine products were obtained in low to moderate yield (35—55%).



Scheme 1.
Stereoselective Synthesis of **25**

Table 1

Optimization Summary[a]



entry	base	"Pd"	solvent	yield
1	NaO*t*Bu	$Pd_2(dba)_3$	Toluene	81%
2	Cs_2CO_3	$Pd_2(dba)_3$	Toluene	38%
3	Cs_2CO_3	$Pd(OAc)_2$	Toluene	63%
4	Cs_2CO_3	$Pd(OAc)_2$	Dioxane	82%[b]

[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 2.3 equiv base, 1 mol % $Pd_2(dba)_3$ (2 mol % Pd) or 2 mol % $Pd(OAc)_2$, 2 mol % Dpe-phos (with $Pd_2(dba)_3$) or 4 mol % Dpe-Phos (with $Pd(OAc)_2$), solvent (0.25 M), 105 °C.

[b] The reaction was conducted at 100 °C.

product	dr	yield[b]
		75

11

product	dr	yield[b]
		82

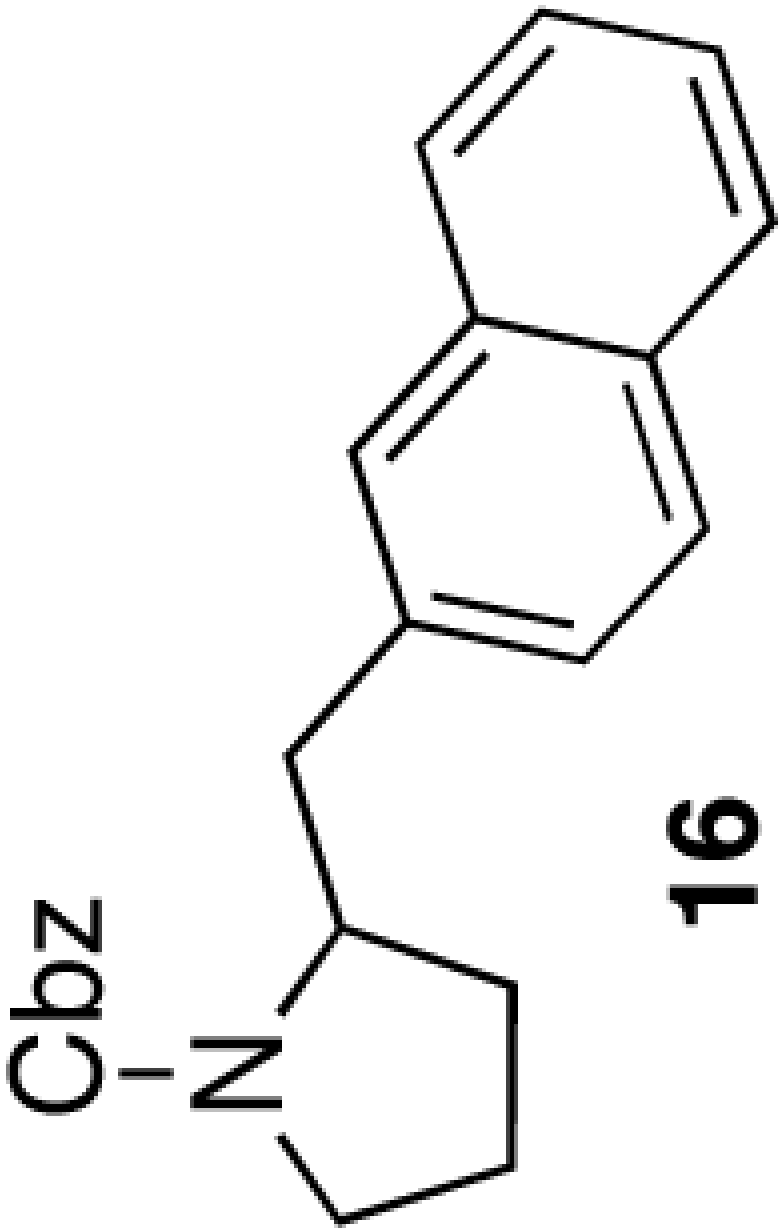
4

product	dr	yield[b]
12		78[e]

product	dr	yield[b]
13		76[e]

product	dr	yield[b]
		79

product	dr	yield[b]
15		76[c,e]

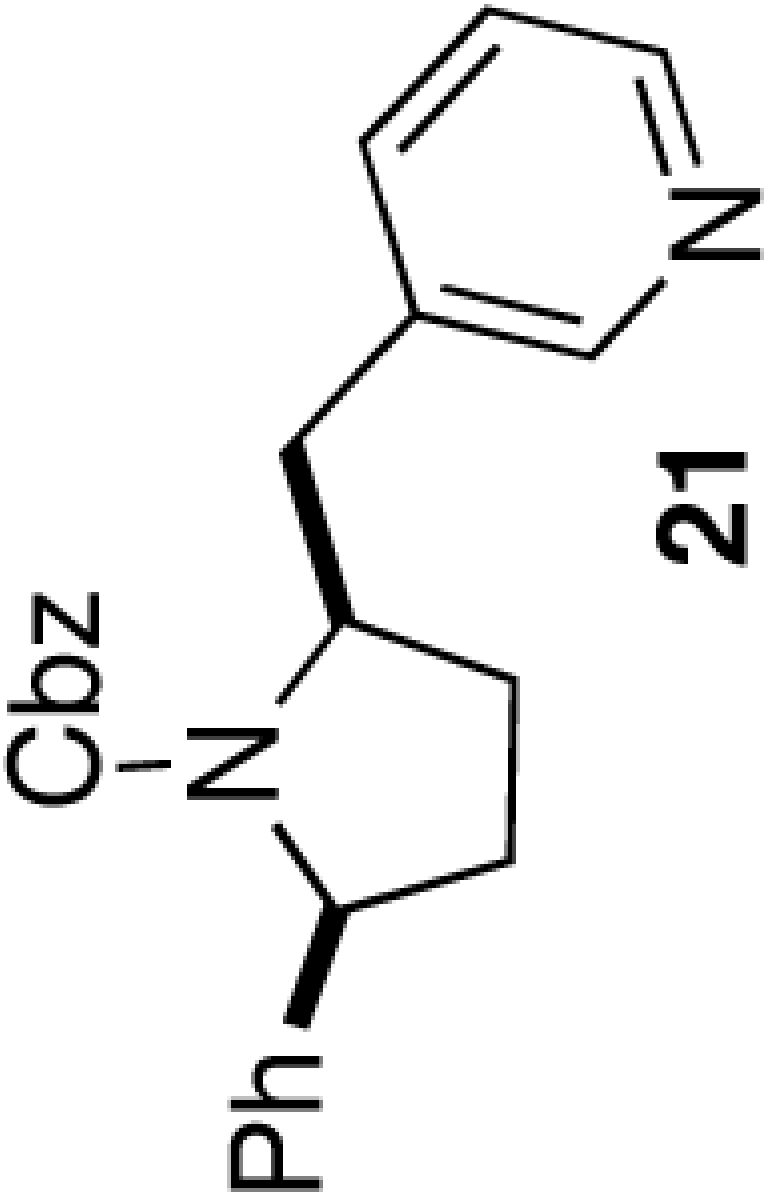
product	dr	yield[b]
	88 17[d]	

product	yield[b]	dr
17	88[c]	—

product	dr	yield[b]
	12:1	80

product	dr	yield[b]
19	15:1	76

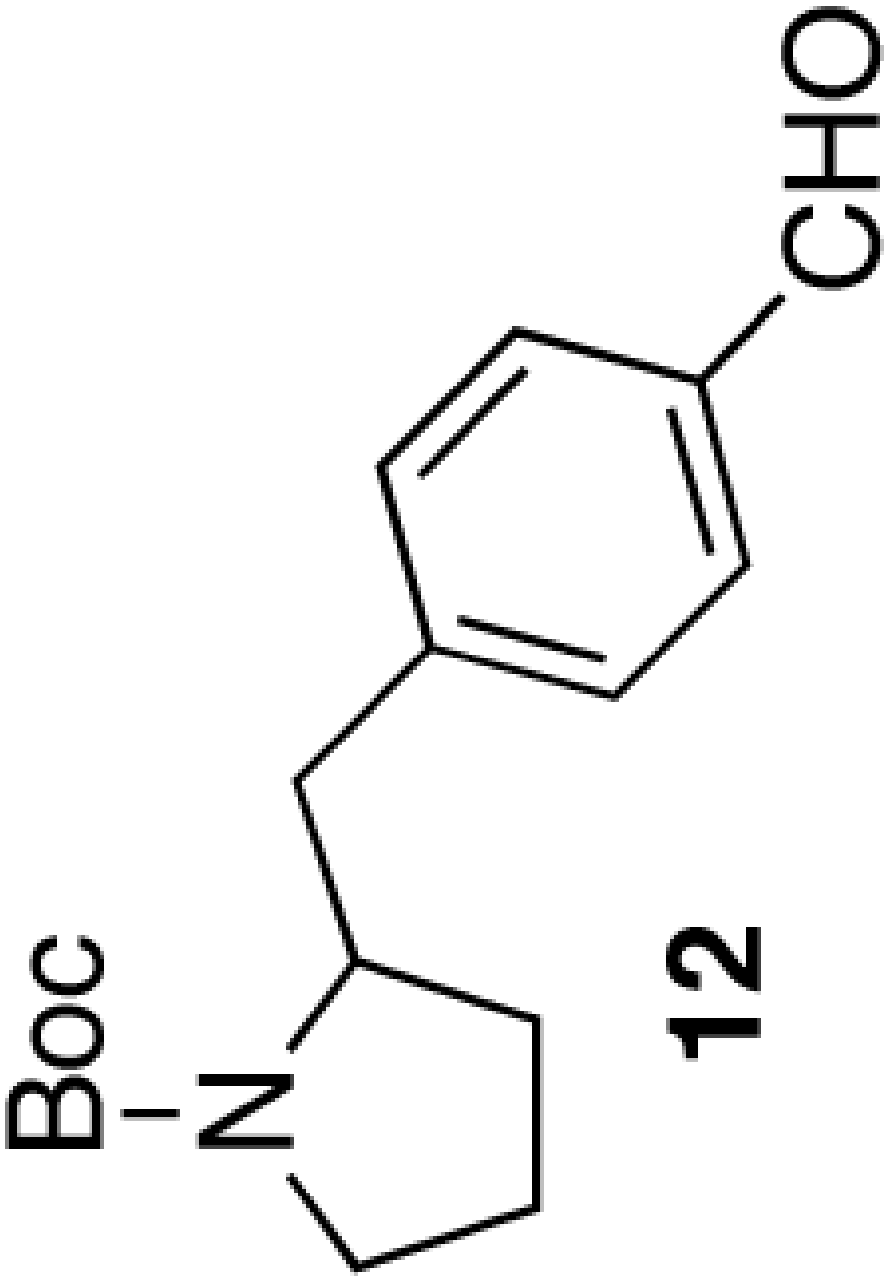
product	dr	yield[b]
20	>20:1	75

product	dr	yield[b]
	>20:1	74

product	dr	yield[b]
	>20:1	71

product	dr	yield[b]
23	>20:1	73

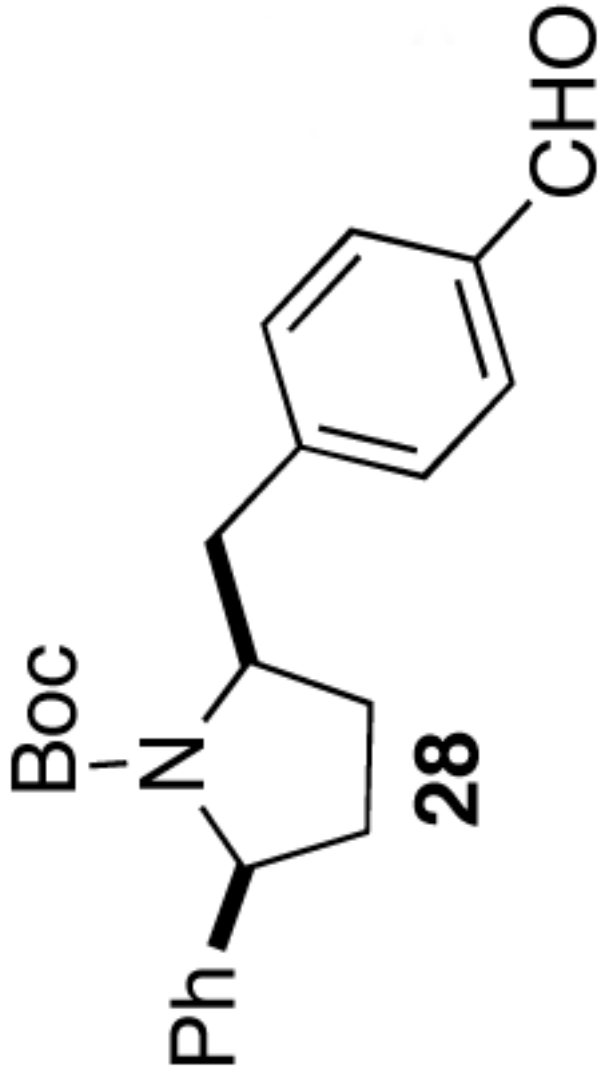
Table 3

product	dr	yield[b]
	—	67%[c]

12

product	dr	yield[b]
26	—	74

product	dr	yield[b]
	12:01	70

product	dr	yield[b]
	>20:1	64

product	dr	yield[b]