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Concise Palladium-Catalyzed Synthesis of Dibenzodiazepines and Structural Analogs

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Abstract

A general and highly efficient protocol for the synthesis of dibenzodiazepines and their structural analogs is reported. In the presence of catalytic quantities of palladium, readily accessible precursors are cross-coupled with ammonia and then spontaneously undergo an intramolecular condensation to form the corresponding dibenzodiazepines in one step. This new strategy is applicable to the construction of a wide variety of dibenzooxazepines and other structurally related heterocycles.

Pharmacologically active dibenzodiazepines and their structural analogs - dibenzooxazepines and dibenzo(di/ox)azepinones,^{1,2} account for a significant portion of a widely prescribed azepine-based drugs. Unfortunately, access to a large number of structural derivatives of these heterocycles is hindered by their multi-step syntheses. Since the first reported synthesis of dibenzodiazepine derivatives by Schmutz in 1964–67 (Clozapine and Loxapine; Figure 1), limited progress has been made.³ Existing routes to dibenzodiazepines (and their derivatives) generally rely on preparation of amide⁴ or lactam⁵ intermediates, and subsequent functionalization of the heterocyclic scaffold to introduce additional substituents (Scheme 1). Such transformations typically require harsh conditions, purification after each synthetic step, and the use of protecting groups.^{1b–c, 5c, 6} Most previously reported synthetic pathways require reduction of a NO₂ group, and have limited functional group compatibility, whereas coupling of substrates with two free NH₂ groups leads to a mixture of products. Thus there is a need for an efficient, concise, and general protocol to provide access to a diverse range of dibenzodiazepine derivatives.

Herein, we report a versatile method for the synthesis of dibenzodiazepine analogs, via formation of key precursor (**1**), which is readily accessed by cross-coupling of *o*-carbonyl(anilines or phenols) with 1,2-dihaloarenes (or their equivalents) (Scheme 2).⁷ This synthetic strategy was based on the notion that, in the presence of catalytic quantities of palladium, this precursor would generate intermediate (**2**) via cross-coupling with ammonia,⁸ and further spontaneously undergo an intramolecular condensation to form the corresponding dibenzodiazepine (**3**) in one step (Scheme 2). We also felt that this new strategy might be applicable to the construction of dibenzooxazepines (**3**; Y=O) or other structural analogs, such as dibenzodiazepinones (**4**; Y=NH) and dibenzooxazepinones (**4**; Y=O). To our knowledge, these constitute the first application of the Pd-catalyzed coupling of ammonia in the synthesis of complex heterocycles.⁸

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ASSOCIATED CONTENT

 Supporting Information. Experimental procedures, characterizations, spectral data for all compounds, and the complete list of authors for citation 2(a). This material is available free of charge via the Internet at <http://pubs.acs.org>.

In order to test our hypothesis, aniline (**5**), which was prepared in 94% yield via a C-N coupling reaction⁷ of 2-aminobenzophenone and 2-bromochlorobenzene, was selected as the diarylamine precursor (Scheme 3). Initial studies were carried out on a 0.5 mmol scale at temperatures ranging from 80–110 °C, and with a variety of palladium sources, bases and phosphines.^{7a, 8c} We found that an efficient catalyst for the desired transformation could be formed from the combination of *t*-BuDavePhos (**L3**), Pd₂(dba)₃ and NaOt-Bu at 85 °C. Other combinations of catalyst, ligand and base (Scheme 3 a, b) led to the reduction of starting precursor (**5**) or gave low yields of desired dibenzodiazepine (**7**). The use of 1,4-dioxane as solvent provided the optimal yield of product and allowed for a convenient protocol to be developed in which a commercially available solution of ammonia (0.5 M in 1,4-dioxane) could be used as the source of NH₂.^{8a} The optimal range of equivalents of ammonia was broad (5 – 10 equivalents; Scheme 3-c), which simplifies the experimental operation. The highest conversion was achieved when five equivalents of NH₃ were employed at 0.1 M concentration of precursor.

In principle, the reaction of precursor **5** with ammonia could produce three possible reactive intermediates (**6a-c**) (Scheme 4) that could give rise to dibenzodiazepine **7**. In order to differentiate among these, the reaction was carried out under standard conditions but in the absence of molecular sieves. Compound **6a** was then isolated as the only observable intermediate and the structure was assigned on the basis of its ¹H and ¹³C NMR and elemental analysis. No evidence for the presence of either a hemiaminal or an imine was detected. It should be also noted that no diarylated product⁸ was formed under the optimized conditions. Presumably, the intramolecular condensation of intermediate **6a** yields **7** faster than an additional intermolecular Pd-mediated cross-coupling with **5**.

We next prepared a range of diarylamine precursors (**8**), that were subjected to our optimized conditions, to provide a range of dibenzodiazepine derivatives in good to excellent yields (Table 1). Notably, both electron-rich and electron-deficient diarylamine precursors were transformed efficiently. Under these conditions, heterocycles such as diaxoles, thiols, pyridines, and various functional groups were tolerated. Interestingly, our optimized conditions failed to provide the desired dibenzodiazepine products in the case of acetophenone-core precursors (R = Me). However, we found that by increasing the amount of ammonia to 7 equivalents, the catalyst loading to 4 mol%, and the temperature to 120 °C, the desired transformation proceeded readily in the presence of Cs₂CO₃, albeit in lower yields (products **9f** and **9g**, Table 1).

With a suitable access to dibenzodiazepines in hand, we next examined the scope of the reaction to form dibenzooxazepines. For this transformation, the key diarylether precursors (**12**) were prepared via copper-catalyzed C-O cross-coupling reactions of commercially available 2-carbonyl-phenols (**10**) and 1,2-dihaloarenes (**11**) (Table 2).^{7d} As expected, in the presence of Pd₂(dba)₃, **L3**, and base (NaOt-Bu or Cs₂CO₃) reactions of such precursors (both electron-rich and electron-deficient) with ammonia afforded the dibenzooxazepines as single products and in good yields (Table 2).

As an expansion of this study, we next explored the preparation of structurally related dibenzodiazepinones and dibenzooxazepinones via a tandem amination-cyclization approach. For this study, commercially available ethyl-2-aminobenzoate and 1-bromo-2-chlorobenzene were chosen as test substrates. Precursor (**14**) was then prepared via a C-N cross-coupling reaction and isolated in 88% yield (Scheme 5). In order to prevent cleavage of the ester functional group, this precursor was subjected to the ammonia coupling reaction conditions in the presence of Cs₂CO₃ as base. As a result, dibenzodiazepinone (**16**) was obtained in 80% yield. On the basis of previous observations, we envisioned that **16** could be generated in a one-pot process via the intramolecular aminolysis of reactive intermediate

15 - resulted from the cross-coupling of **14** with ammonia (Scheme 5). To determine the nature of the intermediate formed, precursor **14** was allowed to react under the optimized conditions for 6 hours. Consequently, **15** was isolated in 47% yield, while no products other than **16** and precursor **14** were observed. It should be noted that strong base, acid or metallic reagents were not required to promote the cyclization of **15**, representing a first case of direct aminolysis in the presence of catalytic amount of palladium.¹⁰ Further investigations using several ester-functionalized precursors (prepared in the same way as **14**) were performed. As shown in Table 3, the cascade transformations were successful and quite general, tolerating variation in substituents of the precursors, and leading to the formation of expected heterocycles in high yields. We were also pleased to find that substrates bearing a wide range of esters, such as tert-butyl, ethyl and methyl, which significantly simplifies the synthetic protocol with regards to the choice of available starting material.

In conclusion, we have developed a practical and general protocol for the Pd-catalyzed synthesis of dibenzodiazepines and their structural analogs, an important class of heteroaromatic compounds. This method is applicable to a wide variety of precursors, and good yields of pure heterocycles were obtained. The synthetic advantage of this route is exemplified by the successful preparation of these compounds via the catalytic and shortest sequence reported to date, and through the use of simple, easily accessible starting materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

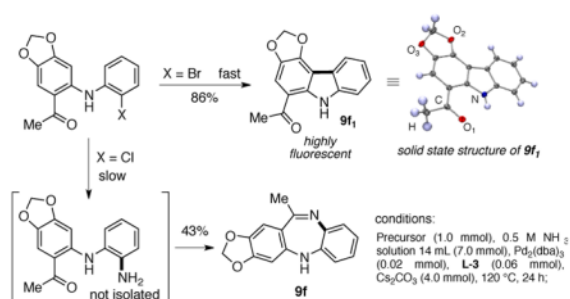
Acknowledgments

This work is supported by an educational donation provided by Amgen and from the National Institutes of Health (Grant No. GM-58160) to whom we are grateful. We also thank FMC Lithium for a generous gift of CIP(*t*-Bu), and Nippon Chemicals for gifts of chemicals and unrestricted funds. We thank reviewer 3 for thoughtful and constructive comments and suggestions concerning the mechanism of formation of **7**.

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7. 2-Chlorophenyl trifluoromethanesulfonate also can be used as a coupling partner (see supporting information). (a) Surry DS, Buchwald SL. *Angew Chem, Int Ed*. 2008; 47:6338–6361. (b) Surry DS, Buchwald SL. *Chem Sci*. 2011; 2:27–50. (c) Hartwig JF. *Angew Chem, Int Ed*. 1998; 37:2046–2067. (d) Maiti D, Buchwald SL. *J Am Chem Soc*. 2009; 131:17423–17429. [PubMed: 19899753] (e) Fors BP, Watson DA, Biscoe MR, Buchwald SL. *J Am Chem Soc*. 2008; 130:13552–13554. [PubMed: 18798626] (f) Hartwig JF. *Acc Chem Res*. 2008; 41:1534–1544. [PubMed: 18681463]
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9. Replacing the chloride atom of precursor, used for preparation of **9f** (Table 1) by bromide, while maintaining all other reaction conditions constant, provided a highly selective cyclization towards carbazole **9f₁** in high yield (86%), completely suppressing the formation of dibenzodiazepine **9f** (for details see supporting information).



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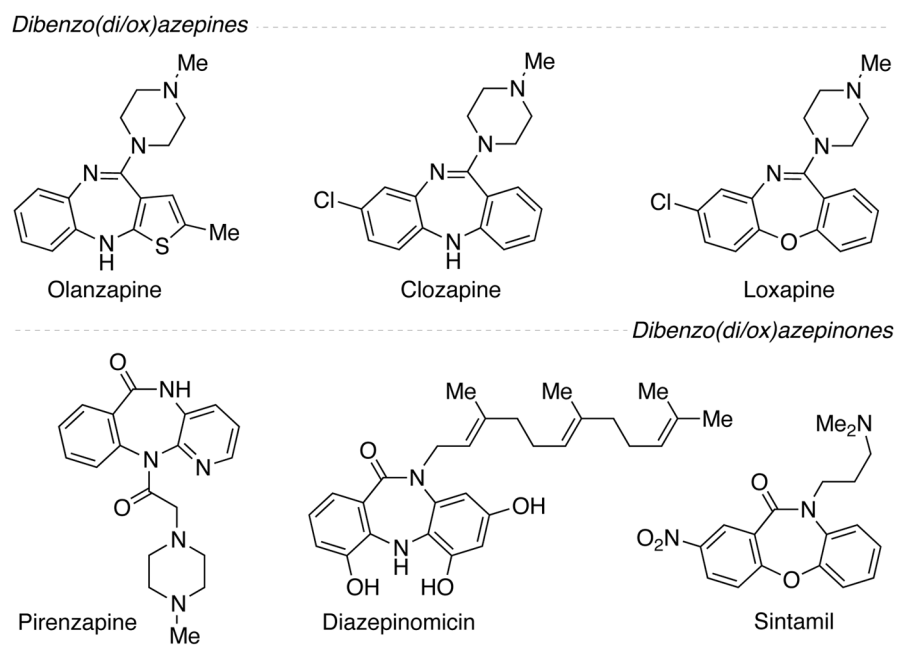
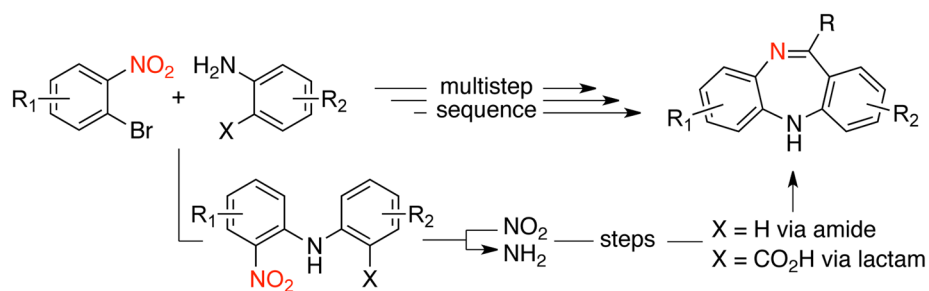
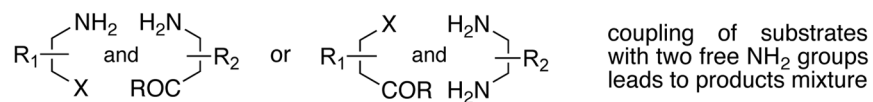


Figure 1.
Pharmacologically active dibenzodiazepine derivatives



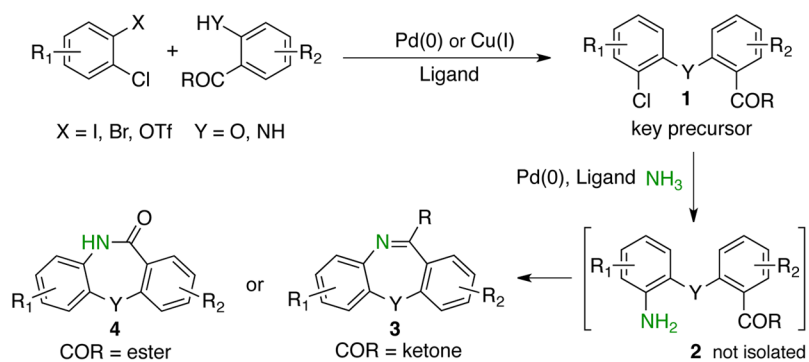
reagents used: POCl_3 , PPA, SOCl_2 , RZnCl , Pd/C, SnCl_2 , Peptide coupling reagents

(Ref. 7)

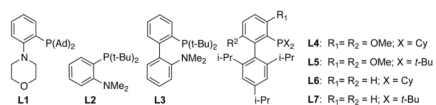
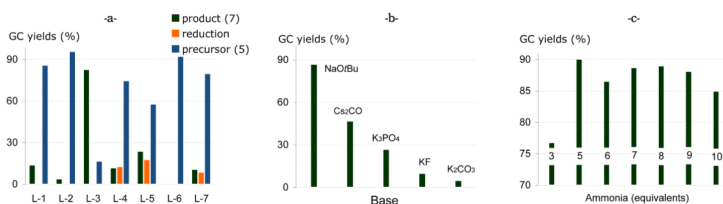
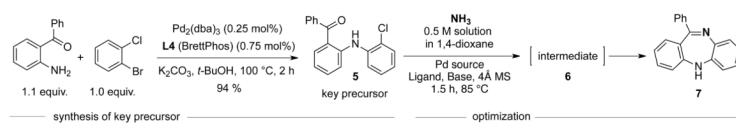


Scheme 1.

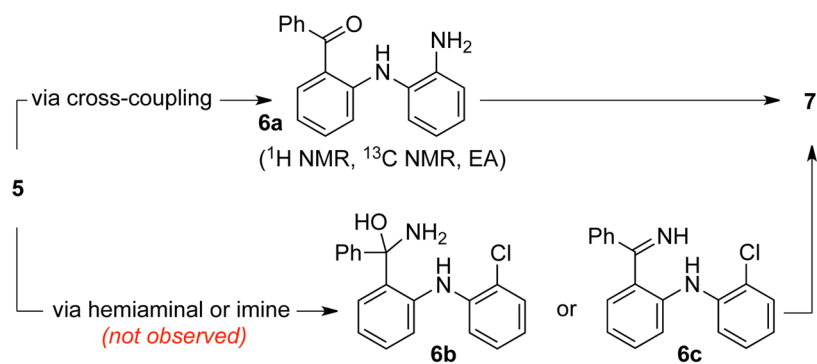
Pairs of coupling partners traditionally used for synthesis of dibenzodiazepines



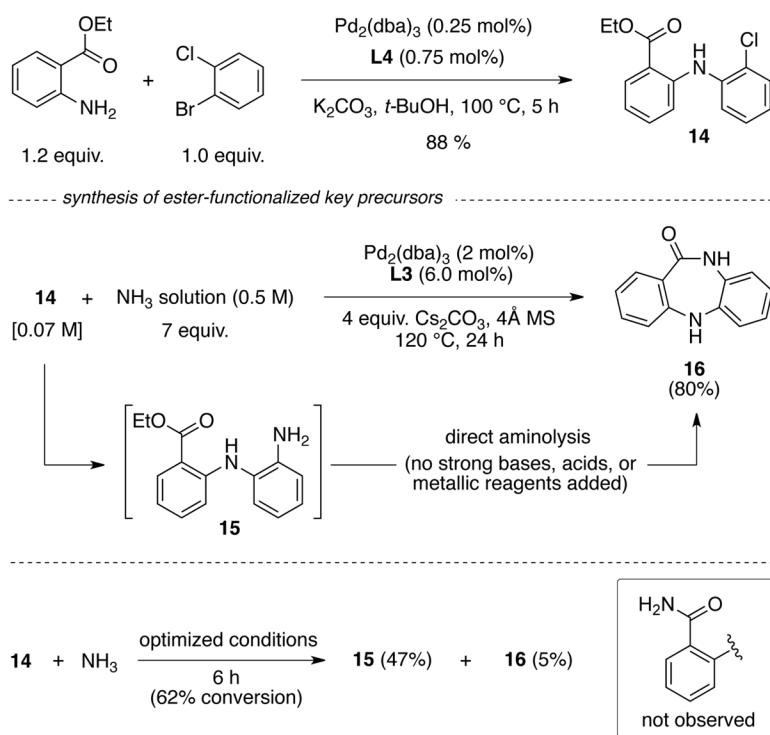
Scheme 2.
Proposed synthesis of dibenzo(di/ox)azepines and dibenzo(di/ox)azepinones



Scheme 3.
 Optimization study for the synthesis of dibenzodiazepines.



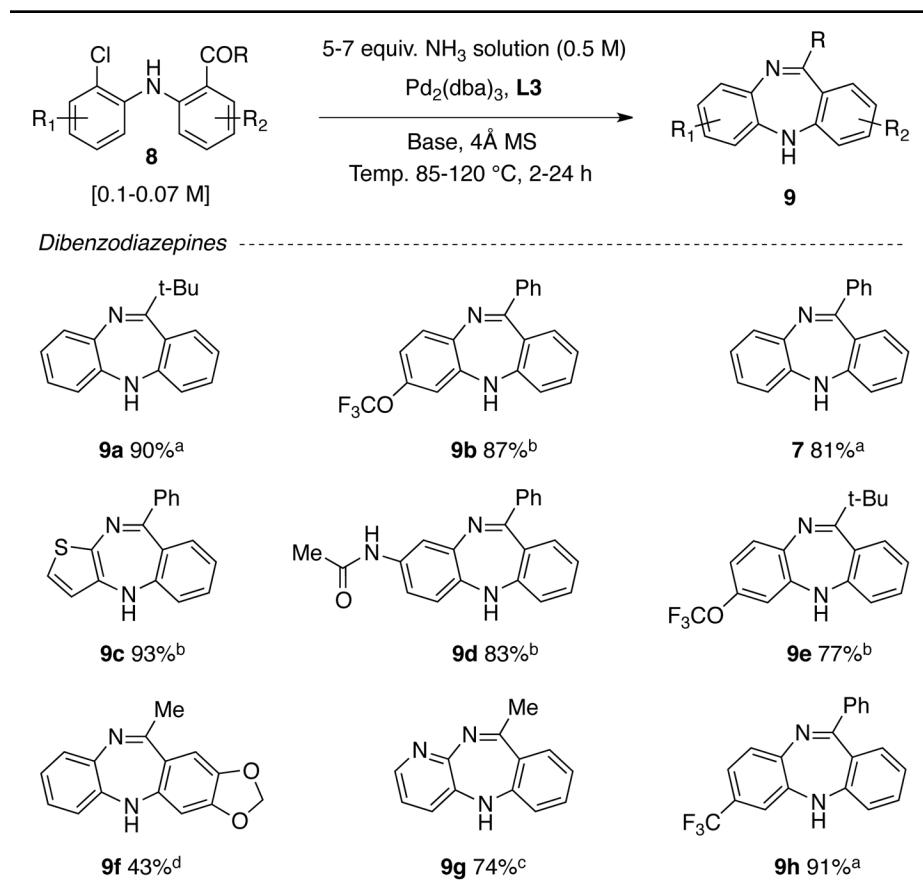
Scheme 4.
Plausible Pathways for the Formation of Dibenzodiazepine



Scheme 5.
Formation of dibenzodiazepinone

Table 1

Palladium-catalyzed synthesis of dibenzodiazepines

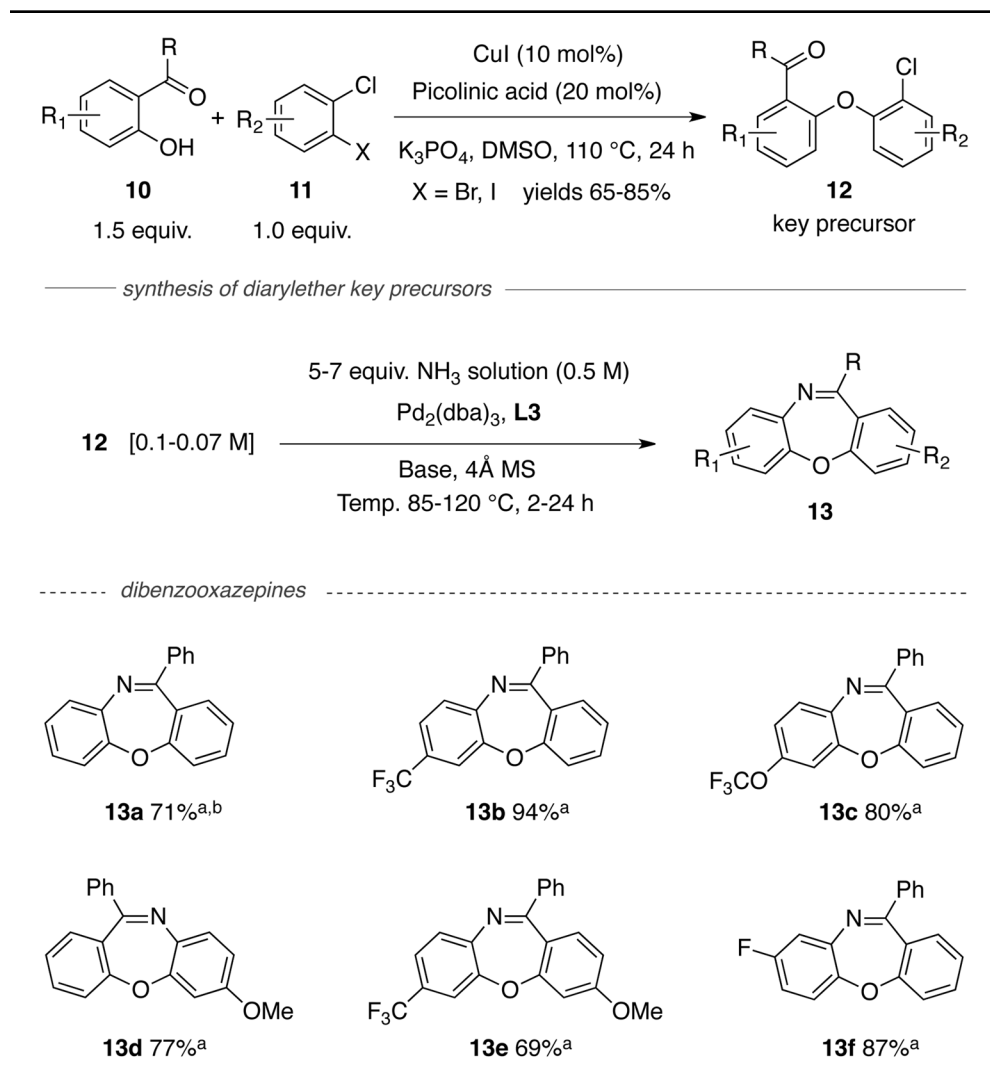


Conditions: yields are an average of 2 runs;

^a precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane 10 mL (5.0 mmol), Pd₂(dba)₃ (0.015 mmol), **L-3** (0.05 mmol), NaOt-Bu (1.5 mmol), 85 °C, 2 h;^b 5 h;^c Precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane 14 mL (7.0 mmol), Pd₂(dba)₃ (0.02 mmol), **L-3** (0.06 mmol), Cs₂CO₃ (4.0 mmol), 120 °C, 24 h;^d Ref. 9.

Table 2

Palladium-catalyzed synthesis of dibenzooxazepines

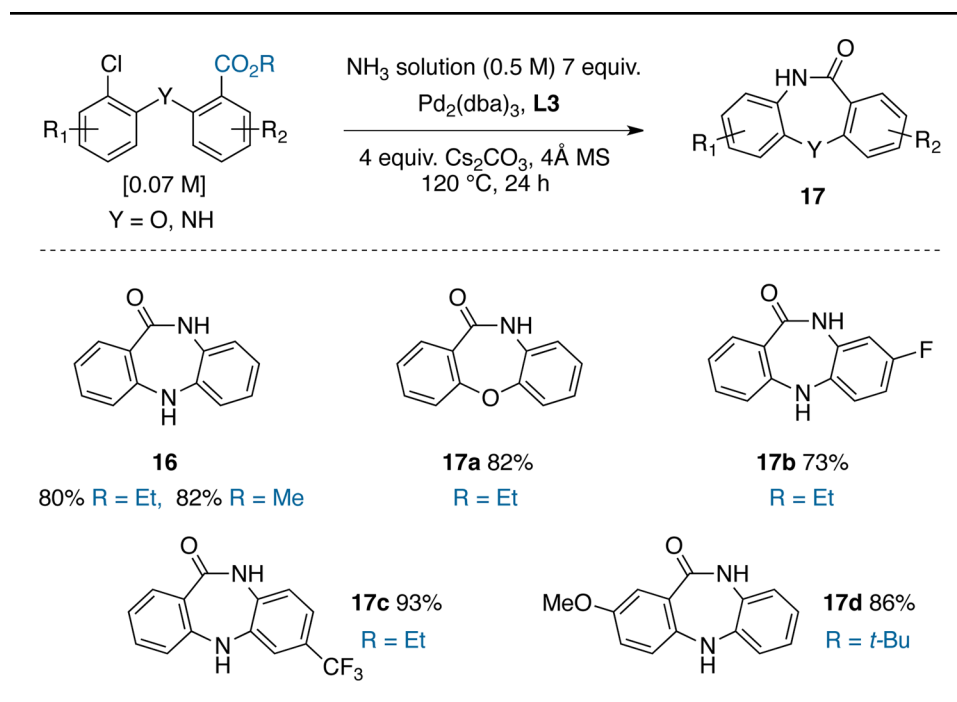


Conditions: yields are an average of 2 runs;

^a precursor (1.0 mmol), 0.5 M ammonia solution in 1,4-dioxane 10 mL (5.0 mmol), Pd₂(dba)₃ (0.015 mmol), **L-3** (0.05 mmol), NaOr-Bu (1.5 mmol), 85 °C, 5 h;

^b Precursor can be prepared from 1,2-dibromobenzene or from 1-bromo-2-iodobenzene.

Table 3

Palladium-catalyzed synthesis of dibenzodiaze-pinones and dibenzooxazepinones^a

Conditions: yields are an average of 2 runs;

^a precursor (1.0 mmol), 0.7 M ammonia solution in 1,4-dioxane 14 mL (7.0 mmol), Pd₂(dba)₃ (0.02 mmol), L-3 (0.06 mmol), Cs₂CO₃ (4.0 mmol), 120 °C, 24 h.