Asymmetric Catalysis

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Elaborating Complex Heteroaryl-Containing Cycles via Enantioselective Palladium-Catalyzed Cycloadditions

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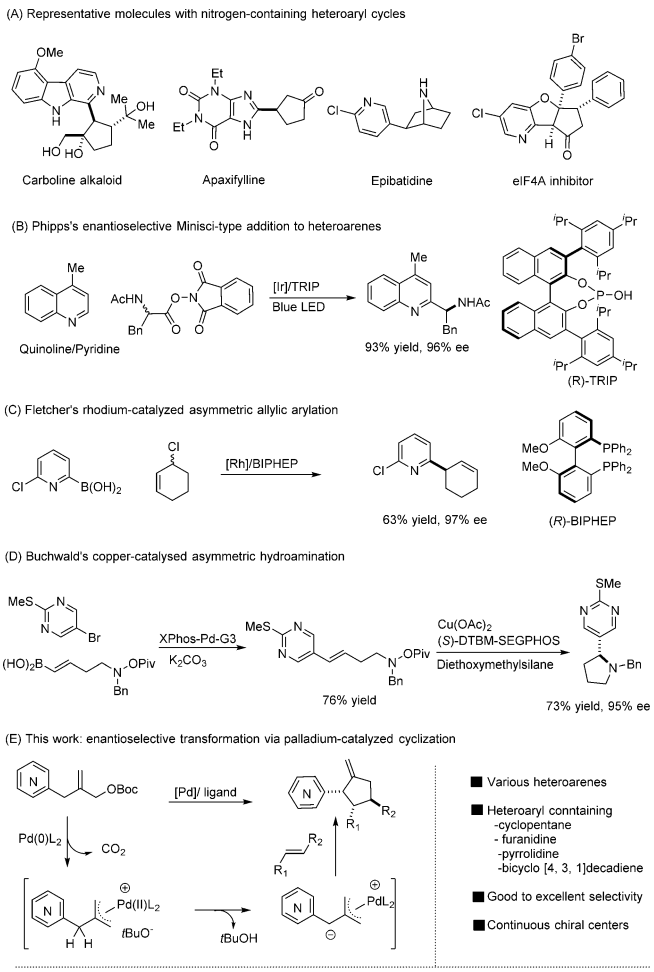
Abstract: *A general method for asymmetric synthesis of heteroaryl-containing cycles via palladium-catalyzed cyclization is reported. Most classes of nitrogen-containing aromatics, including pyridines, quinolines, pyrimidines, various azoles and the derivatives of nucleobases are compatible substrates, offering various heteroaryl-substituted cyclopentane, pyrrolidine, furanidine and bicyclo[4.3.1]decadiene derivatives with good to excellent enantioselectivity and diastereoselectivity.*

Introduction

Due to their distinctive pharmacological properties—including improving therapeutic potency, lowering drug lipophilicity, increasing aqueous solubility, and reducing the inhibition of cytochrome P450s et al.[1]—approximately half of the top 200 pharmaceuticals sold worldwide contain heteroaromatic and heteroaliphatic cyclic rings.[2] In the library of heterocylic compounds, the heteroaryl-substituted carbo- and heterocycles are of particular importance. Such compounds are widely found not only in natural products, but also marketed drugs and lead candidates (Scheme 1 A).[3] Recently, the demand for chiral and three-dimensional cyclic compounds has substantially increased in the field of medicinal chemistry.[4] To meet this growing demand, together with the potentials and unique properties of heteroaromatics, development of efficient atom-economic methods to build chiral heteroaryl-substituted cycles from readily available starting materials is challenging yet highly attractive.

Direct functionalization of heteroarenes is an efficient method to construct heteroaryl-containing cycles and has become an active area of research over the past decade. Numerous novel reagents as well as innovative reaction systems have been developed to facilitate synthesis of heteroaryl-containing building blocks and bioactive compounds.[5] However, catalytic asymmetric transformations in this area are rather unexplored, especially for the synthesis of chiral heteroaryl-substituted cycles. One significant breakthrough was reported by Phipps et al. in 2018, which described a Minisci-type addition of α-amino radicals to heteroarenes via synergistic catalysis.[6] However, only pyridines and quinolines were employed, and no cyclic radical source was reported (Scheme 1 B).



Scheme 1. Selected examples for molecules bearing nitrogen-containing heteroaryl cycles; representative enantioselective examples; and our catalytic asymmetric cycloaddition.

Recently, Fletcher et al. reported a rhodium-catalyzed asymmetric allylic arylation between aryl boronic acids and cyclic allylic halides.[7] However, for building nitrogen-containing heteroaryl products, only C2-substituted pyridyl boronic acid gave acceptable results (Scheme 1 C). Another example is Buchwald's copper-catalyzed intramolecular hydroamination.[8] However, despite having high enantioselectivity, only less commonly-used nitrogen-containing heteroarenes were reported and the products are generally restricted to α-heteroarylpyrrolidines (Scheme 1 D).

Intermolecular cycloaddition reaction is a useful tool to generate complex ring systems with continuous stereogenic centers; the power of which can be witnessed in total synthesis

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of numerous natural products and therapeutic agents.[9] Palladium-catalyzed intermolecular trimethylenemethane (TMM) cycloadditions are versatile methods for the construction of, most notably, heavily substituted 5- but also 7-, and 9-membered rings.[10] Our group has a longstanding interest in designing and developing new reaction partners. Recently, the use of chiral phosphoramidite and diamidophosphite ligands has shown good success in CN- and imine-substituted asymmetric TMM cycloadditions via in situ deprotonation.[11] Could nitrogen bearing heterocyclic rings be sufficiently electron withdrawing to serve as the activating substituent towards deprotonation of the TMM donor? The high metallophilicity of the nitrogen of heteroarenes might hinder the formation of the active TMM species, rendering the corresponding cycloadditions more challenging. Until now no example of a nitrogen-containing heteroaryl TMM was reported with good results.[12] In spite of these concerns, the ease of accessibility of the requisite TMM donors induced us to pursue the experiment. Herein, we present our results on the palladium-catalyzed enantioselective construction of heteroaryl-containing carbo- and heterocycles (Scheme 1 E).

Results and Discussion

tert-Butyl (2-(pyridin-2-ylmethyl)allyl) carbonate **1a**, which can be readily prepared from commercially available pyridine *N*-oxide in one step in 68% yield was chosen as the model TMM donor (see SI). For the model acceptor, chalcone **2a** was employed. As shown in Figure 1, $CpPd(\eta^3\text{-}C_3H_5)$

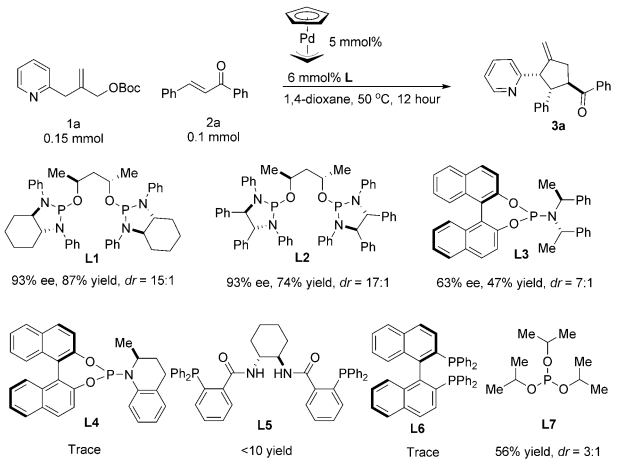

Figure 1. Ligand effect of the model reaction.

ligated by the chiral bis-diamidophosphite ligand **L1** delivered an excellent 93% *ee* and good 87% yield. Similar stereoselectivities were obtained using **L2** albeit with slightly lower yield. Subsequent examination showed that the identities of the ligand and palladium source are crucial for the reactivity. When palladium acetate was used, the enantioselecitivity decreased significantly. For the ligand part, phosphoramidite ligand **L3** gave modest 64% *ee* and 47% yield, whereas **L4** only gave trace amount product with significant decomposition. Bisphosphine ligands, including **L5** and **L6**, also showed minimal reactivity. Finally, achiral phosphite **L7** could affect the reaction in moderate yield and *dr*, which led us to select this achiral ligand for the preparation of racemic samples. After detailed solvent screening, 1,4-dioxane offered the best results, while THF and toluene gave lower yield and *ee* values, respectively (details see SI) (Figure 2).

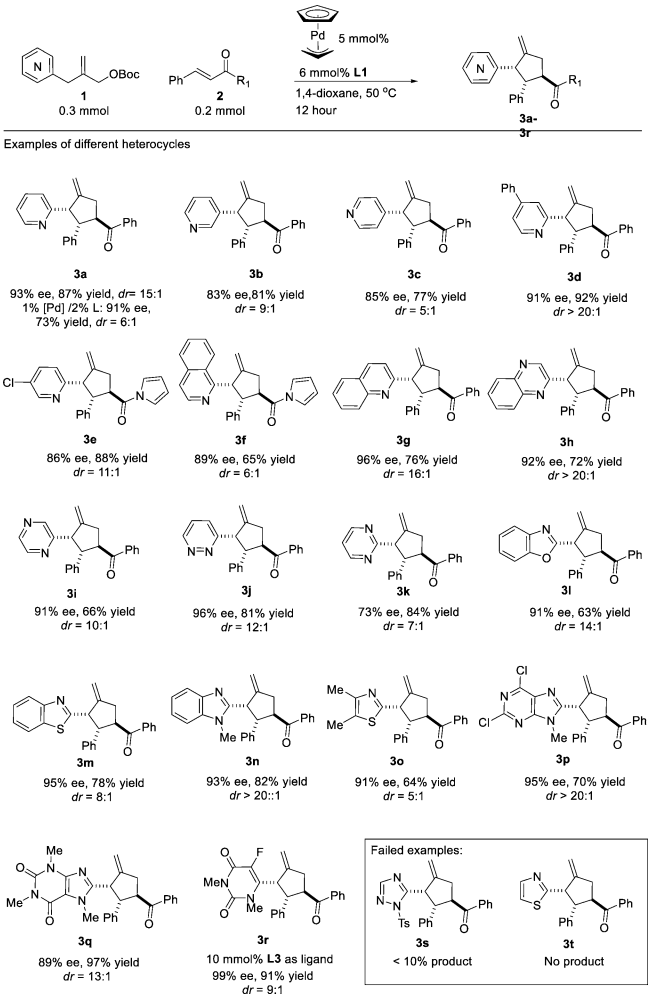

Figure 2. Examples of different nitrogen-containing aromatic heterocycles.

With the optimized conditions in hand, we first focused on TMM donors with six-membered nitrogen-containing heteroarenes. As far as we know, the C2 position is needed for the asymmetric functionalization of α position of pyridine.[13] Recently, 3-pyridyl substituted cycles were found to be important CYP11B2 inhibitors,[14] so moving the TMM motif from the C-2 to the C-3 and C-4 position of pyridine would have important significance. Delightfully, the two pyridine regioisomers bearing the TMM motif on the C3 (**1b**) and C4 (**1c**) position successfully reacted to give **3b** and **3c** with only slightly lower *ee* and *dr* values. The higher reactivity of regioisomer **1b** compared to **1c** suggests that an inductive effect outweighs any resonance effect. Chlorine, a useful handle in various cross-coupling reactions, was also compat-

ible in our reaction system (**3e**). Sterically hindered substrates were also tolerated, offering isoquinolyl- and quinolylcyclopentane (**3f** and **3g**) in excellent enantio- and diastereoselectivity. With the success of the mononitrogen-containing heteroaryl TMM, we then turned our attention to substrates bearing multiple nitrogens. Heterocycles bearing multiple nitrogens are important elements in fine and bulk chemical fields and medicinal chemistry,[15] however, current methods to construct stereogenic centers bearing a polynitrogen-containing heteroaryl moeity are extremely limited.[5b,16] Delightfully, 2-quinoxalinyl (**3h**), 2-pyrazinyl (**3i**) and 2-pyridazinyl (**3j**) donors all gave the desired products with good yields and excellent ee's, except for 2-pyramidinyl **3k**, which gave a moderate 73% *ee*.

Our next targets were the five-membered azole species, which were not as readily reactive as the six-membered counterparts. Nonetheless, benzoxazole, benzothiazole and *N*-methyl-benzoimidazole donors gave good yields and excellent selectivities (**3l, 3m** and **3n**). Although 4, 5-dimethylthiazolyl cyclopentane (**3o**) was obtained with good *ee* and *dr*, simple C2-thiazolyl substituted donor offered only a trace amount of product, presumably due to the acidic C–H bond on the thiazole can quench the catalytic cycle (**3t**). The failure of triazolyl substrate may also because of the acidic proton (**3s**). Biologically important heteroarenes were also examined. Using Knochel's protocol,[17] TMM donors with purine, caffeine and uracil derivatives can be readily prepared. To our delight, highest 99% *ee* value could be obtained for the 5-F-uracyl substrate (**3r**) with 91% yield, and nearly quantitative yield was observed for the caffeinyl substrate (**3q**), which can be attributed to the strong electron-withdrawing nature of the carbamide group, hence facilitating the deprotonation process. Finally, choro-substituted purine is also well-tolerated, generating the corresponding cyclopentane with 95% *ee* and 70% yield (**3p**). Simple phenyl and electron-rich *N*-CO_2Me-2-indolyl TMM precursors were also subjected to the above standard conditions, however, no desired products can be detected by ^{1}H NMR. This impelled us to develop new strategies to figure out these problems and perfect the TMM system in the future.

Having demonstrated the success using different heteroaryl TMM donors, we then studied the scope of the acceptors (Figure 3). Firstly, acyclic C=C double bonds bearing different functional groups were subjected to the optimized conditions (Figure 3a). Model substrate **1a** reacted readily with various chalcone derivatives bearing both electron-deficient and electron-rich aryl rings (**4a**–**4e**). Other electron-withdrawing groups (R_2) were also examined. Nitro (**4f**, **4k** and **4l**), *N*-acyl pyrrole (**4g** and **4l**), acyl imidazole (**4j**), sulfone (**4m**), and azlactone (**4n**) all gave good to excellent results, offering a broad library of chiral pyridyl-substituted cyclopentanes. The R_1 group not only can be phenyl rings, but also 2-furanyl (**4d**), 3-pyridyl (**4e**), ferrocenyl (**4f**), methyl (**4h**), alkynyl (**4i**) and imine (**4l**). Interestingly, addition to the conjugated diene substrate occurred at the Y, δ double bond of the substrate to give adduct **4h** as the major product, presumably due to the steric hindrance of the adjacent pyridyl motif. α-Methyl-β-nitro styrene was also suitable for current conditions,

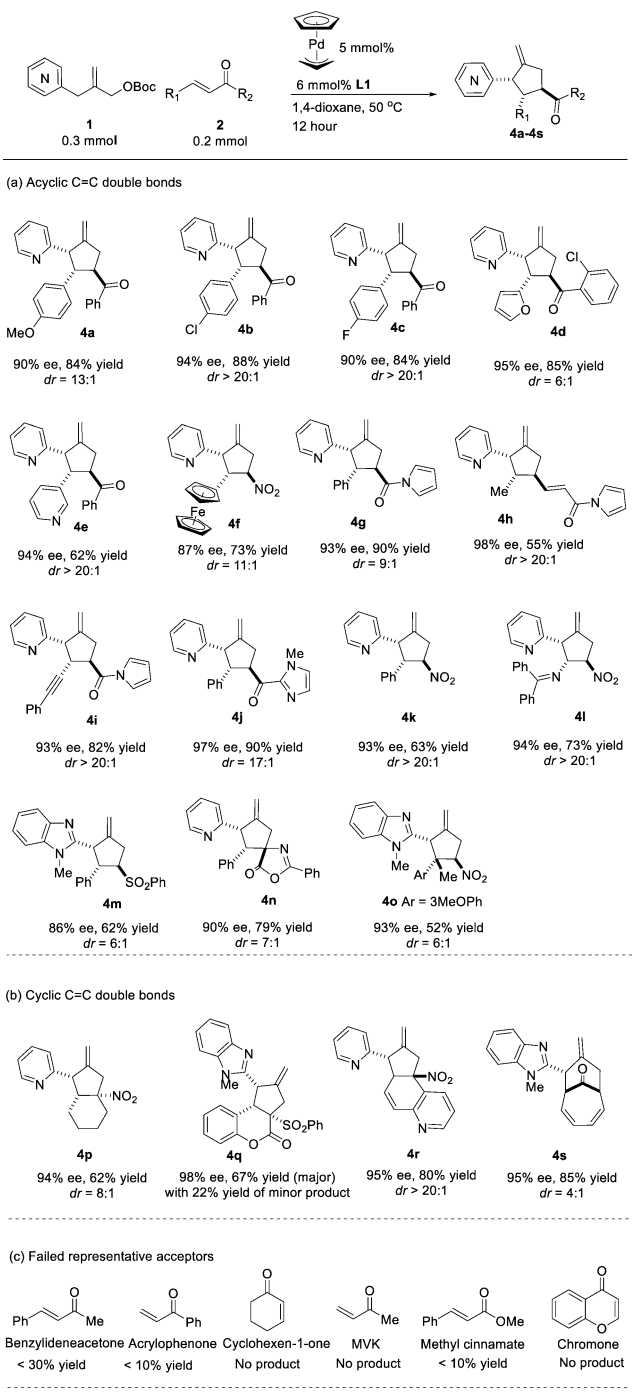

Figure 3. Examples of different electron deficient C=C acceptors.

generating a quaternary carbon center containing cyclopentane derivative with slightly lower yield (**4o**).

Cyclic alkenes (Figure 3b) such as 1-nitrocyclohexene and 3-phenylsulfonylcoumarin were successfully employed with lower diastereoselectivity compared to the acyclic counterparts (**4p**, **4q**). Dearomative cyclization was also successful with 8-nitroquinoline as the acceptor, and the desired fused ring was obtained with excellent yield, *ee* and *dr* (**4r**). Besides [3+2] cyclization, a highly selective [6+3] cyclization with tropone delivered bicyclo[4.3.1]decadiene in 95% *ee* and 85% yield (**4s**). Finally, the absolute configuration of **4m** was

determined by X-ray crystallography (see SI). The stereochemical outcome for all other cycloadducts was assigned by analogy.

The acceptors bearing acidic C–H bonds, such as benzylideneacetone, cyclohexen-1-one and MVK, did not give acceptable results under current conditions perhaps due to the acidity of the TMM acceptors. The substituent at the β position of the acceptor is needed to inhibit the self-polymerization. In the example of acrylophenone, the alkene was consumed very quickly to give a black mixture with trace amount of desired product by H NMR. Some other examples such as methyl cinnamate and chromone were also tested, only to give trace amount of desired products (Figure 3c).

The reaction is not restricted to electron-deficient olefins. Imines and carbonyl compounds also afforded the desired cyclic adducts (Figure 4). Several representative *N*-Cbz aryl

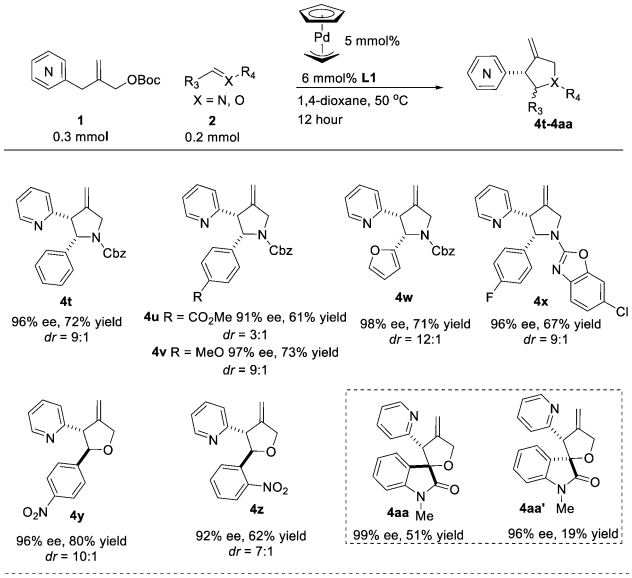

Figure 4. Examples of different representative electron deficient C=N and C=O acceptors.

imines were examined. Both electron-donating and electron-withdrawing groups on the imine aryl group were well-tolerated to afford the desired 3-pyridyl pyrrolidines (**4t**–**4w**) with good results. Notably, utilization of *N*-heteroaromatic imine to generate **4x** provides an expedient and asymmetric route to important candidates in medicinal chemistry.[18] To demonstrate the activity of C=O double bond, aromatic aldehydes with electron-deficient groups were subjected to the reactions. 3-Pyridyl tetrahydrofurans could be generated with good stereoselectivities (**4y** and **4z**); however, aldehydes bearing electron-donating and neutral aryl groups generally gave poor yields. *N*-Methyl isatin was also compatible for our reaction, offering **4aa** with an excellent 96% *ee* albeit with a lower *dr* compared to other carbonyl acceptors. The relative configuration of adducts with C=O bond was assigned as "*trans*", which was supported by NOE.

To gain insight into the roles the heterocycles attached to the TMM donor may play; a 4-nitro phenyl TMM precursor which lacks any nitrogen atom on the aromatic ring was synthesized and subjected to the reaction conditions (Figure 5a). In combination with the results of C2-pyridyl (**3a**), C3-pyridyl (**3b**) and C4-pyridyl (**3c**), the observations reinforce the importance of electron withdrawing rings play for reactivity. On the other hand, the modest 74% *ee* observed in Figure 5a despite many attempts to improve the *ee* value suggest that some coordination with nitrogen which is present in large amounts relative to palladium center may affect the chiral recognition.

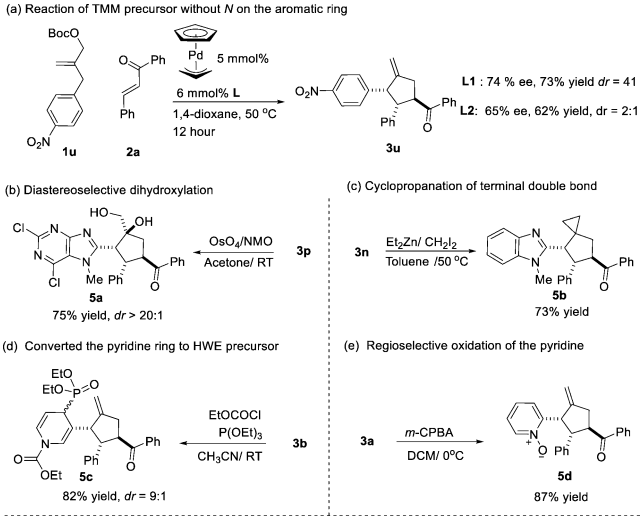

Figure 5. Mechanistic study and derivatization of the products.

The exocyclic olefin of the products could be utilized as a versatile handle for structural elaboration. For example, dihydroxylation of **3p** offered diol **5b** as a single diastereomer (Figure 5b). Simmons–Smith cyclopropanation of **3n** generated spirocyclic **5b** in 73% yield (Figure 5c). Nucleophilic addition of triethoxyphosphite to the in situ generated pyridonium cation generates HWE ylide precursor **5c** (Figure 5d). In addition, selective oxidation of the pyridine ring in the presence of the terminal olefin gave pyridine *N*-oxide **5d** in 87% yield, which is a useful directing group for the functionalization of pyridine (Figure 5e).[19]

Conclusion

In conclusion, we have developed an efficient method for the construction of chiral heteroaryl-substituted cycles via palladium-catalyzed asymmetric cycloaddition. In all of these cases, the requisite TMM intermediates are generated by a simple deprotonation (Scheme 1E), which greatly simplifies the availability of the TMM precursors, increasing the predictability of this method. Various heteroaryl-containing cyclopentanes, pyrrolidines, furanidines and bicyclo-[4.3.1]decadiene derivatives can be easily obtained from readily available materials. Due to the unique properties of heteroarenes, the new synthetic method described here is expected to serve as a useful tool in the discovery of new therapeutics and agrochemicals.[20] Furthermore, the presence

of an exocyclic olefin motif of the obtained products provides a powerful handle for further structural elaborations.

Experimental Section

A 5 mL vial was flame-dried with a magnetic stir bar inside, (*R,R,S,S,R,R*)-Cy-Tom ligand **L1** (8.4 mg, 5 mmol%.), CpPd(η^3-C_3H_5) (2 mg, 5 mmol%), chalcone (43 mg, 0.2 mmol) and *tert*-butyl (2-(pyridin-2-ylmethyl)allyl) carbonate (75 mg, 0.3 mmol) were added and the system was placed under an atmosphere of argon. The system was then dissolved in dry 1,4-dioxane (1.0 mL) and stirred at RT for 10 min, then the mixture was placed in an oil bath maintained at 50 °C for 12 h. Filtration through a plug of silica gel gave the crude reaction mixture, which was concentrated in vacuo and subjected to ^{1}H NMR to determine the diastereomeric ratio (*dr*). After measuring the *dr*, the crude mixture was subjected to flash silica column chromatography (petroleum ether/EtOAc/TEA 80:20:0.5) to yield the title compound (**3a**, 59 mg, 87% yield, *dr* = 15:1) as a light-yellow oil.

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Conflict of interest

The authors declare no conflict of interest.

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