Site-Selective C—H Functionalization of *N*-Aryl and *N*-Heteroaryl Piperidines, Morpholines and Piperazines Controlled by a Chiral Dirhodium Tetracarboxylate Catalyst

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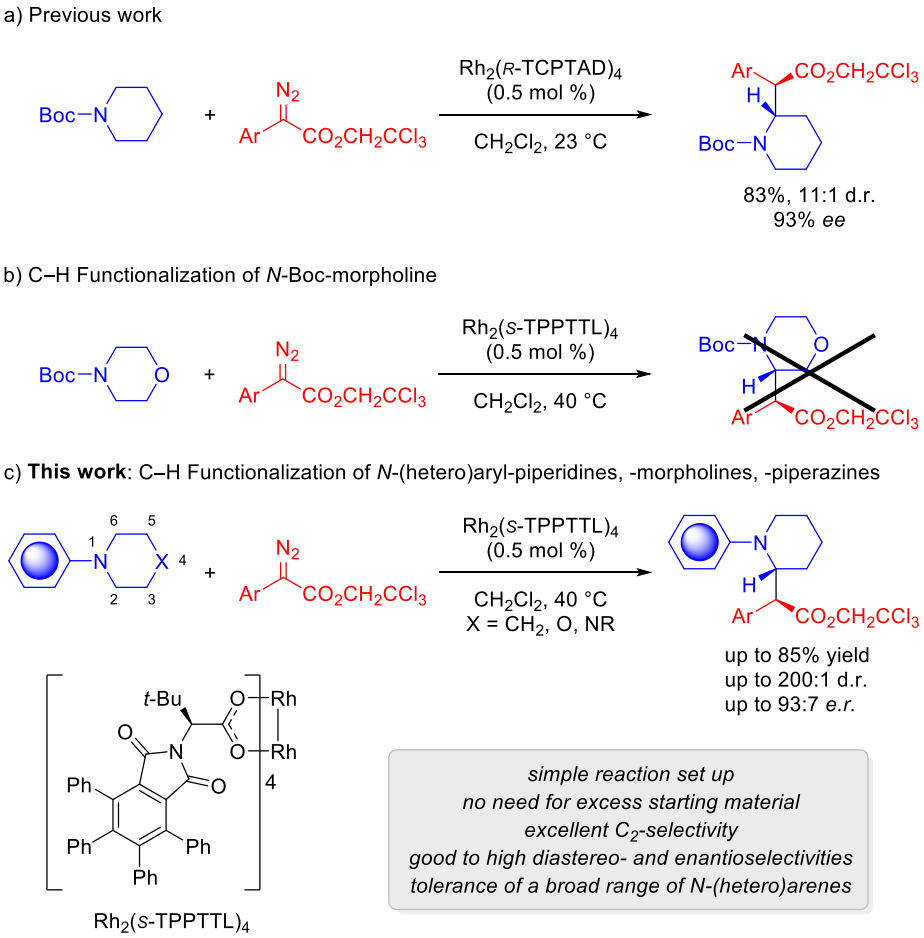
KEYWORDS C—H functionalization, piperidines, morpholines, piperazines, stereoselectivity, regioselectivity, rhodium.

ABSTRACT: Rhodium-catalyzed C—H insertion by donor/acceptor carbenes is a highly atom-economical synthetic tool. However, the site-selectivity of the C—H transformation on the target molecule is often a major issue. Site-selective C—H functionalizations of challenging substrates like *N*-aryl- and *N*-heteroaryl piperidines could be achieved through chiral rhodium carbene intermediates, leading to the formation of highly stereoselective C-2 products. In addition, *N*-aryl morpholines and piperazines were selectively reacted at the α position to the *N*-aryl group.

C—H Functionalization offers an attractive strategy to access novel scaffolds for further derivatization into potential drug candidates.[1-4] One such transformation is the rhodium-catalyzed insertion of aryldiazoacetates into C—H bonds by means of rhodium carbene intermediates.[5] The site-selectivity of the reaction can be controlled by choosing the appropriate catalyst and several chiral catalysts have been developed capable of achieving these reactions with high levels of asymmetric induction. The utility of the methodology to generate chiral scaffolds has been illustrated by means of functionalization of cyclobutanes,[6] silacycloalkanes[7] and bicyclopentanes.[8] Reactions are preferred at electron-rich sites but this tendency can be overcome by using sterically crowded catalysts.[9,10] In general, sites α to oxygen and nitrogen are electronically preferred, whereas sites β to oxygen and nitrogen are disfavored due to the electron-withdrawing inductive effects.[11]

Considerable interest has been shown in developing methods for the site-selective functionalization of piperidine as it is a privileged scaffold for drug discovery.[12-19] The rhodium-carbene approach was studied early on during the seminal work on intermolecular C—H functionalization, because the reaction at C-2 of piperidine with a phenyldiazoacetate is a quick entry to the pharmaceutical drug methylphenidate.[20-22] Recently, site-selective C—H functionalization on *N*-protected piperidine rings was controlled by different chiral dirhodium catalysts for C-2 and C-4 selectivities.[23] The reaction of *N*-Boc piperidine with trichloroethyl aryldiazoacetate was catalyzed by C_4 symmetric catalyst, Rh_2(*R*-TCPTAD)$_4$, delivering highly site-selective C-2 product with good diastereo- and enantioselectivities (Scheme 1a). In the same report, Rh_2(*R*-TPPTTL)$_4$ also provided a good stereoselective outcome for the reaction of 1-[(4-bromophenyl)sulfonyl]piperidine. Under similar reaction conditions, we observed no conversion in the reaction of *N*-Boc morpholine catalyzed by Rh_2(*S*-TPPTTL)$_4$ (Scheme 1b). This represents a classic example of a system where the deactivating β-substituent interferes with activation influence of the α-substituent.[11,23] Therefore, we decided to determine, whether it would be possible to design systems in which C—H functionalization would occur even in the presence of a β-substituent. We reasoned that the nitrogen group would need to be more electron-donating than the *N*-Boc group that is typically used but cannot be a regular amine because it would react with the carbene or poison the catalyst. Previously, we had shown that *N,N*-dimethylanilines were susceptible to C—H functionalization[24] and so we explored *N*-aryl piperidines, morpholines, and piperazines as substrates (Scheme 1c). Notable features of our strategy include (i) simple reaction set up (ii) with 1:1 stoichiometric ratio of starting material, (iii) excellent regioselectivity at C_2 or α-C position to nitrogen atom, (iv) good to high diastereo- and enantioselectivities, and (v) tolerance of a broad range of *N*-(hetero)aryl substrates.

Scheme 1. C—H Functionalization by chiral dirhodium catalyst

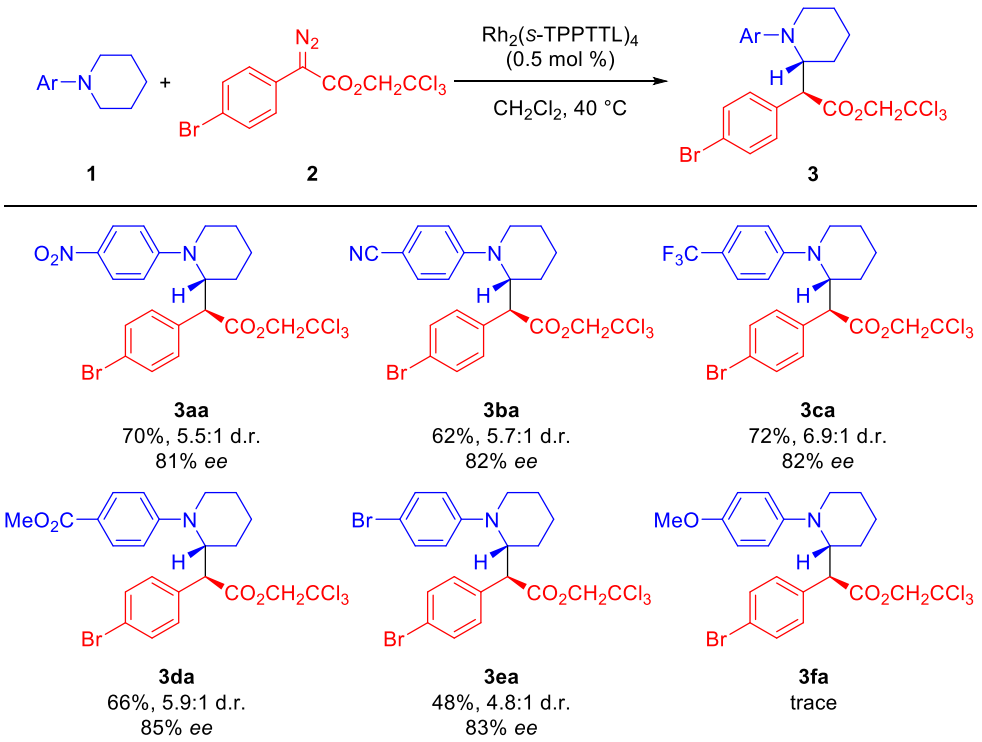


We commenced our studies by examining the C—H functionalization of *N*-arylpiperidines **1** with 1,1,1-trichloroethyl (4-bromophenyl)diazoacetate (**2a**) using Rh_2(*S*-TPPTTL)$_4$ as the catalyst, as shown in Scheme 2. The trichloroethyl derivative was used because it tends to give higher yields and enantioselectivity in C—H functionalization reactions compared to the standard methyl ester.[25] Electron-deficient *N*-arylpiperidines **1a**–**1e** were smoothly converted to the desired C-2 products **3aa**–**3ea**, with good to high diastereo- and enantioselectivities, whereas electron-rich derivative **1f** failed to provide any product **3fa**. Presumably, this lack of reactivity is because the nitrogen is too electron rich and will interfere with the catalyst. The C—H transformation proved to be tolerant of a broad range of valuable functional groups, including nitro (**3aa**), cyano (**3ba**), ester (**3da**), and halide groups (**3ea**).

Inspired by the preliminary results of piperidine derivatives **1**, we replaced electron-poor aryl groups with heteroaryl groups, which are more valuable groups in pharmaceutical chemistry. The reaction of 5-bromo-2-(piperidin-1-yl)pyrimidine (**1g**) under the condition of slow addition of diazo compound **2a** over 90 min gave the expected product **3ga** in high yield with a diastereomeric ratio of 12:1 (Scheme 3). Further simplification and optimization of the reaction led to the following conditions: use of 1:1 stoichiometric ratio of compounds **1g** and **2a**, and one-portion addition of diazo compound **2a**, significantly increasing the yield of the corresponding product **3ga** with a similar level of diastereoselectivity.

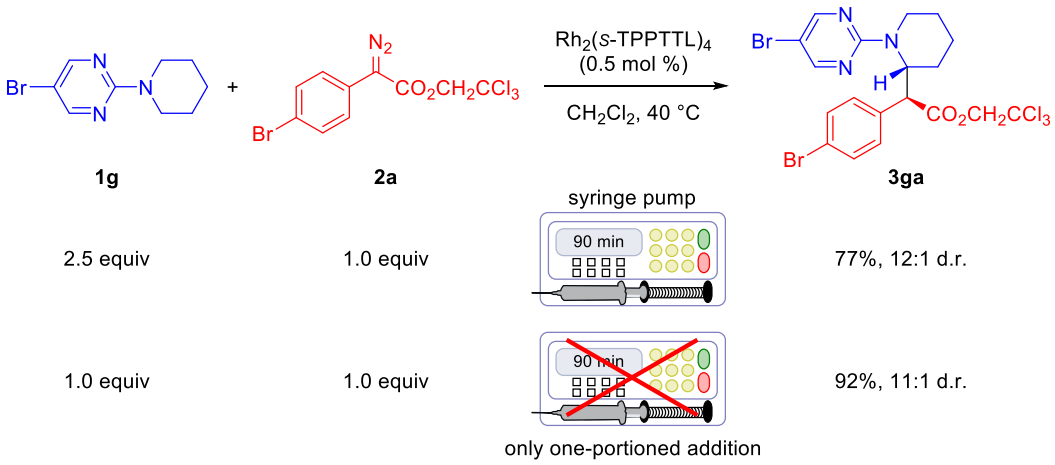
Having the optimized reaction conditions for site-selective C—H functionalization of piperidine derivatives in hand, we then explored the scope of *N*-heteroarylpiperidines **1** (Scheme 4). The dirhodium catalytic reaction proved to be applicable to a wide range of heteroaryl groups, including pyridines (**3ha**), pyridazines (**3ia**), pyrimidines (**3ga**), pyrazines (**3ja**–**3la**), and purines (**3ma**). The site-selectivity and stereoselectivity of the thus-obtained product **3ga** was unambiguously confirmed by X-ray crystal structure analysis. Afterwards, the scope of trichloroethyl aryldiazoacetates **2** was investigated. 2-Naphthyl (**2b**) and *p*-substituted aryl groups (**2c**–**2d**) furnished the C-2 products **3jb**–**3jd** in good yields with high levels of diastereo- and enantioselectivities, whereas 3,4-disubstituted aryl groups resulted in slightly decreased enantioselectivities in their products **3je**–**3jf**. The reaction of 1,1,1-trichloroethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (**2g**) led to the formation of the corresponding product **3jg** in high stereoselectivity, albeit in low yield. While the reaction of 3-bromophenyl diazo compound **2h** showed a significant decrease in stereoselectivity, the reaction of 2-bromophenyl diazo compound **2i** delivered the C-2 product **3ji** as essentially a racemate. The product **3jj** was obtained with a moderate level of enantioselectivity when 2-fluoropheyl diazo compound **2j** was employed in the reaction. It is noteworthy that the steric hindrance of substituents on arenes at the *ortho*- and *meta*-position has a great influence on the stereoselectivity of the corresponding product **3**.

Scheme 2. Site-selective and stereoselective C—H functionalization of *N*-arylpiperidines



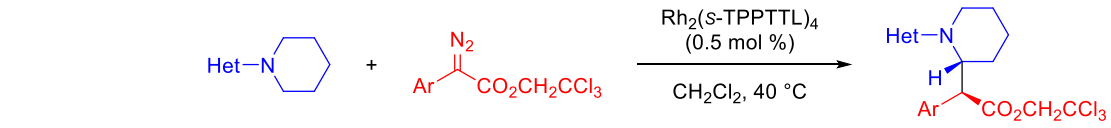
Reaction condition: **1** (0.75 mmol), **2** (0.30 mmol), Rh_2(*S*-TPPTTL)$_4$ (0.5 mol %), CH_2Cl_2 (5 mL), 40 °C, 1 h.

Scheme 3. Simplified reaction set up for stereoselective C—H functionalization

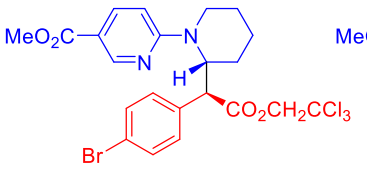


Reaction conditions: **1g** (x equiv), **2a** (0.30 mmol), Rh_2(*S*-TPPTTL)$_4$ (0.5 mol %), CH_2Cl_2 (5 mL), 40 °C. Yields and diastereomeric ratio (d.r.) were determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

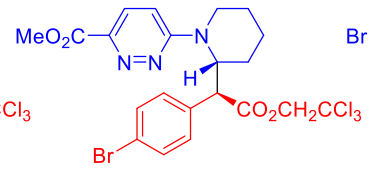
Scheme 4. Dirhodium-catalyzed regioselective C—H functionalization of *N*-heteroarylpiperidines



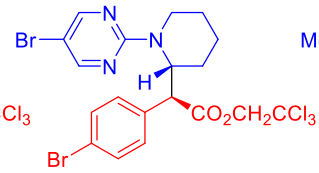
1 **2** **3**



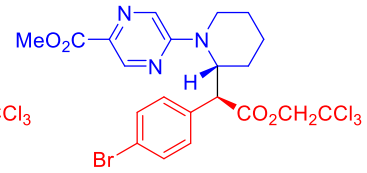
3ha
56%, 10:1 d.r.
81% *ee*



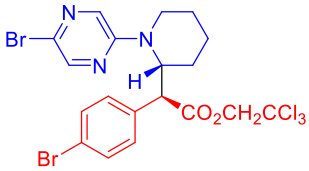
3ia
63%, 14.8:1 d.r.
85% *ee*



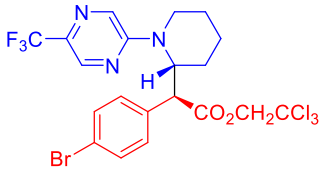
3ga
74%, 11:1 d.r.
74% *ee*



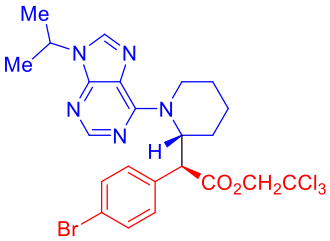
3ja
70%, 30.4:1 d.r.
81% *ee*



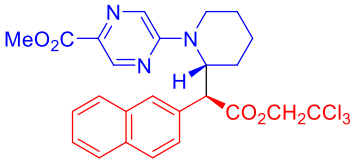
3ka
71%, 11.4:1 d.r.
79% *ee*



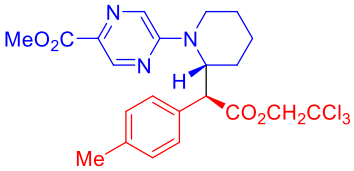
3la
75%, 36:1 d.r.
83% *ee*



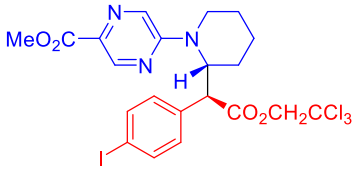
3ma
85%,15.6:1 d.r.
61% *ee*



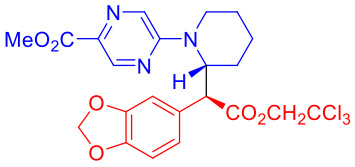
3jb
70%, 45.2:1 d.r.
81% *ee*



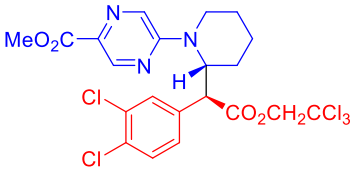
3jc
73%, 51.8:1 d.r.
80% *ee*



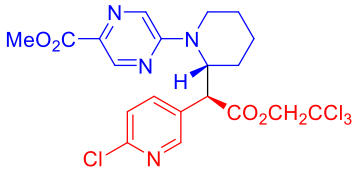
3jd
72%, 24.4:1 d.r.
77% *ee*



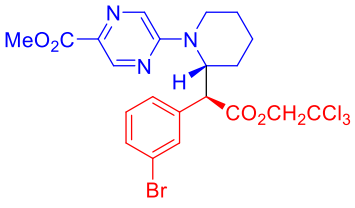
3je
62%, 138:1 d.r.
55% *ee*



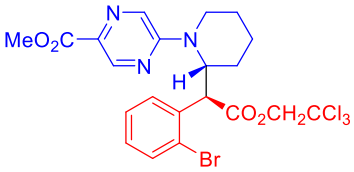
3jf
67%, 29.4:1 d.r.
73% *ee*



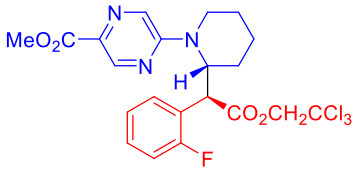
3jg
27%, 3.7:1 d.r.
83% *ee*



3jh
69%, 52.6:1 d.r.
21% *ee*



3ji
63%, 2.9:1 d.r.
6% *ee*



3jj
68%, 16:2 d.r.
51% *ee*

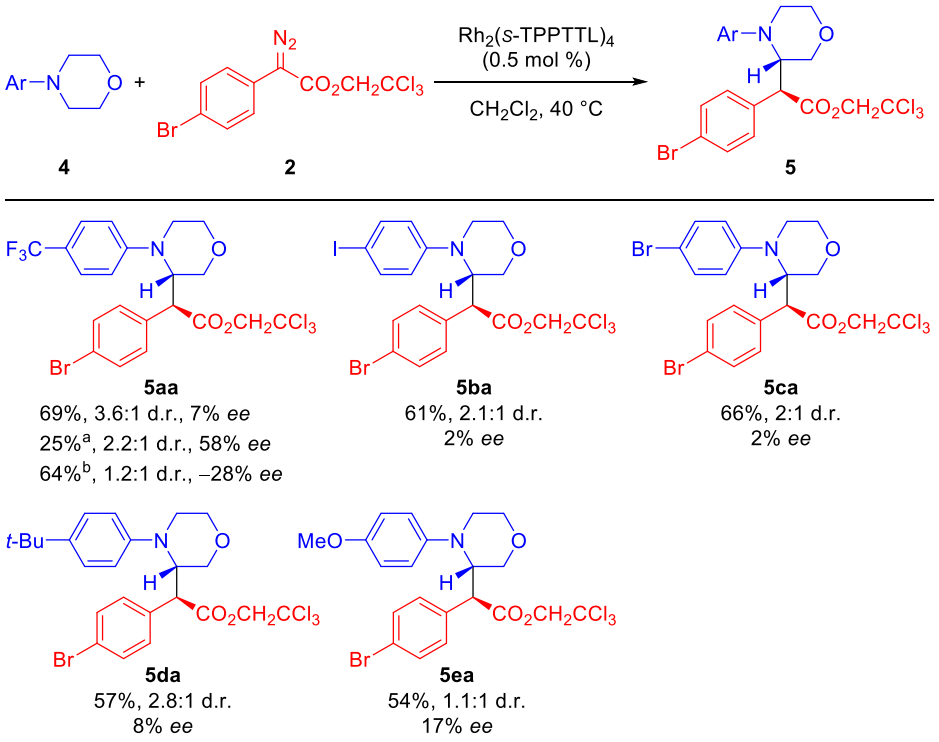
Reaction condition: **1** (0.30 mmol), **2** (0.30 mmol), Rh_2(*S*-TPPTTL)$_4$ (0.5 mol %), CH_2Cl_2 (5 mL), 40 °C, 1 h.

Having established the reaction on *N*-arylpiperidines, we examined the reaction of *N*-arylmorpholines. We were delighted to observe that these substrates were susceptible to C—H functionalization α to nitrogen. Thus, the working hypothesis that the use of a less

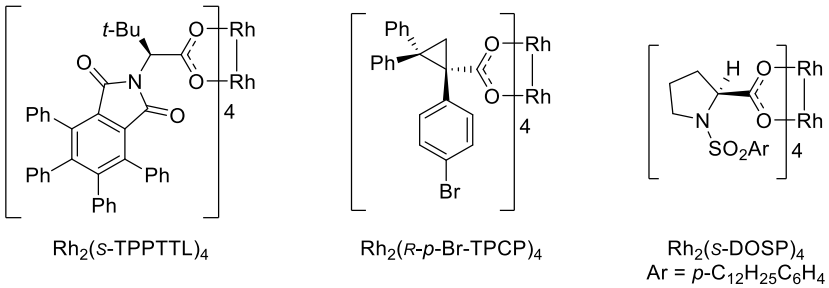
electron-withdrawing group at the nitrogen does allow C—H functionalization to occur even in the presence of electron-withdrawing β-heteroatoms is valid. Electron-rich and electron-poor substituents on *N*-arylmorpholines **4** provided the corresponding C-2-substituted products **5** in moderate to good yields (Scheme 5). Unfortunately, the reactions are no longer highly stereoselective as both the diastereoselectivity and enantioselectivity with all substrates are low. To ameliorate the stereoselectivity outcome of morpholine products **5**, we investigated other commercially available chiral dirhodium catalysts in this transformation. It was found that Rh_2(*R*-*p*-Br-TPCP)$_4$[25] furnished the corresponding C-2 product **5aa** with a moderate level of enantioselectivity, albeit lower yield. This generally offers the potential for achieving the desired outcome for a given substrate of interest by matching it with a suitable catalyst and reaction conditions.

Even though *N*-arylmorpholines are capable of generating the C—H functionalization products, the overall yield and stereochemical outcome is very different from the results with *N*-arylpiperidines. We wondered whether the C—H functionalization of morpholines **4** may not be proceeding by the traditional C—H insertion mechanism (transition state **C**, Scheme 6).[26] The C—H bond may be sufficiently deactivated by the β-oxygen that rhodium-nitrogen-ylide (intermediate **D**) forms instead. A subsequent proton transfer would generate iminium **H** and enolate intermediate **F**/**G** that would react together to form the formal C—H insertion product **5**.

Scheme 5. Site-selective C—H functionalization of *N*-arylmorpholines



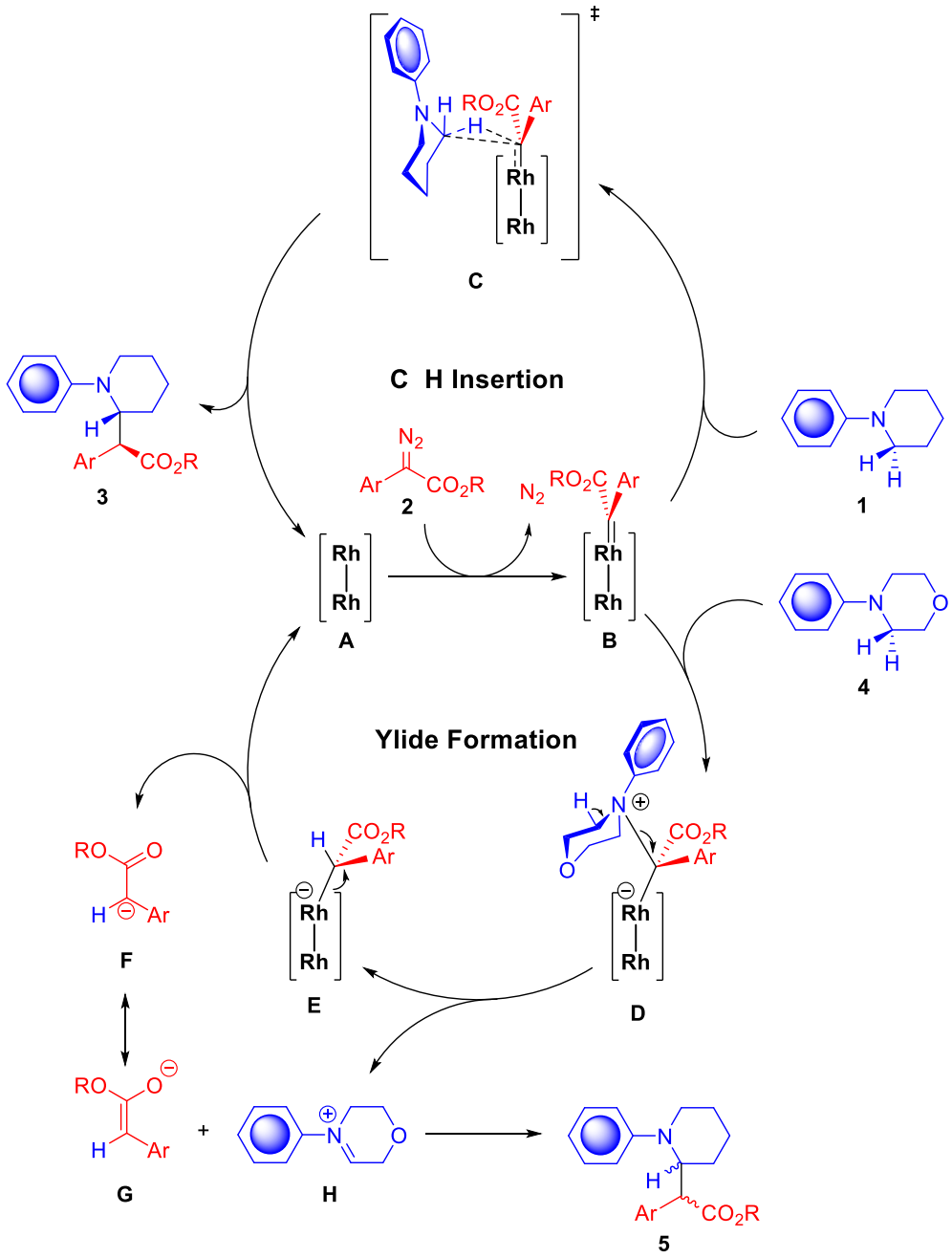
Reaction condition: **4** (0.30 mmol), **2** (0.30 mmol), Rh_2(*S*-TPPTTL)$_4$ (0.5 mol %), CH_2Cl_2 (5 mL), 40 °C, 1 h. [a] Rh_2(*R*-*p*-Br-TPCP)$_4$ and [b] Rh_2(*S*-DOSP)$_4$ were used instead of Rh_2(*S*-TPPTTL)$_4$.



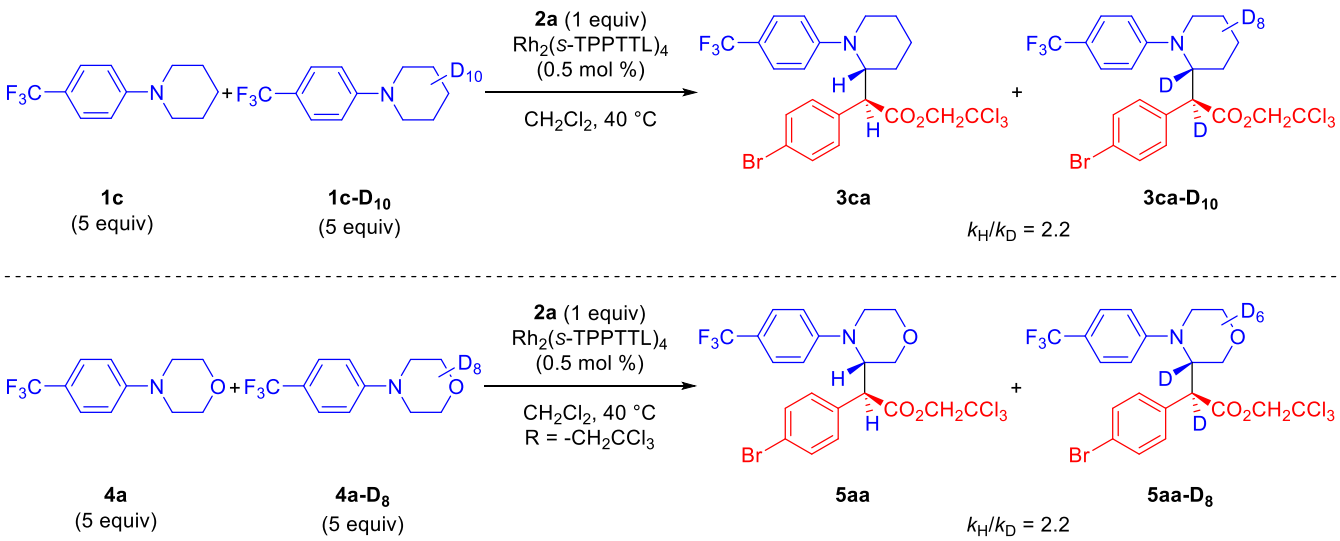
To test this hypothesis, we performed intermolecular competition KIE experiments (Scheme 7). Both experiments of piperidines (**1c** and **1c-D$_{10}$**) and morpholines (**4a** and **4a-D$_8$**) gave KIE values of 2.2. These are similar to the typical value for the reaction with cyclohexane, which cannot involve ylide intermediates.[27] Therefore, we propose both reactions proceed through a direct C—H functionalization reactions but the nature of the substrate has a profound influence on the stereoselectivity of the reaction.

The catalyst-controlled C—H functionalization was also effective on the diaryl-substituted piperazine **6** (Scheme 8). The reaction was highly site-selective, forming the C—H functionalization product **7** in moderate yield and with a moderate level of stereoselectivity. The reaction preferentially occurs at the site adjacent to the more electron-rich *N*-aryl group, which would be expected to be most effective at stabilizing positive charge build up during the C—H functionalization.

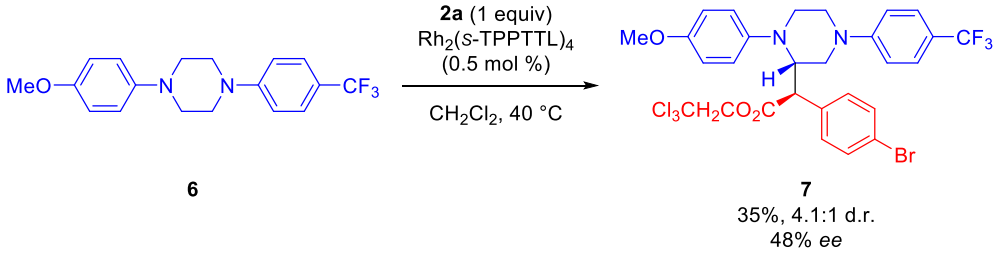
Scheme 6. Catalytic cycles for C—H insertion and ylide formation



Scheme 7. Kinetic isotope effects



Scheme 8. Site-selective C—H functionalization of *N,N′*-diarylpiperazines



Reaction condition: **6** (0.30 mmol), **2a** (0.30 mmol), Rh_2(*S*-TPPTTL)$_4$ (0.5 mol %), CH_2Cl_2 (5 mL), 40 °C, 1 h.

In summary, we reported a general method for site-selective C—H functionalization of *N*-(hetero)aryl piperidines, morpholines, and piperazines via a simple reaction set up and in a highly atom-economical manner. The transformation occurred regioselectively at the α C—H bond next to the nitrogen atom, even though the β heteroatom bond in morpholines and piperazines would deactivate this position. The reaction of piperidines delivered highly stereoselective outcomes. Extension of the method, however, to morpholines and piperazines furnished lower levels of stereoselectivities with the systems tested. This work further illustrates the potential of C—H functionalization by donor/acceptor carbenes controlled by dirhodium tetracarboxylate catalysts and demonstrates its use for the rapid synthesis of pharmaceutically relevant chiral scaffolds.

ASSOCIATED CONTENT

Accession Codes

The following crystal structure has been deposited in the Cambridge Crystallographic Data Centre: **3ga** (CCDC 2203157). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 902 1223 336033.

Supporting Information

Completing experimental details and spectral data of the compounds generated.

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes:

Conflict of Interest: Korkit Korvorapun, Thomas Maier, Armin Bauer, Thomas Licher, John Macor, Volker Derdau are (or were) employees of Sanofi and may hold shares of the company. HMLD is a named inventor on a patent entitled, Dirhodium Catalyst Compositions and Synthetic Processes Related Thereto (US 8,974,428, issued March 10, 2015). The other authors have no competing financial interests.

Data Availability: The data underlying this study are available in the published article and its online supplementary material.

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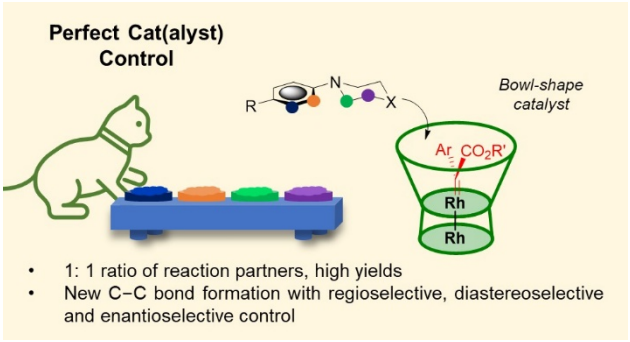
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