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Iridium-Catalyzed Regio- and Diastereoselective Synthesis of C-Substituted Piperazines

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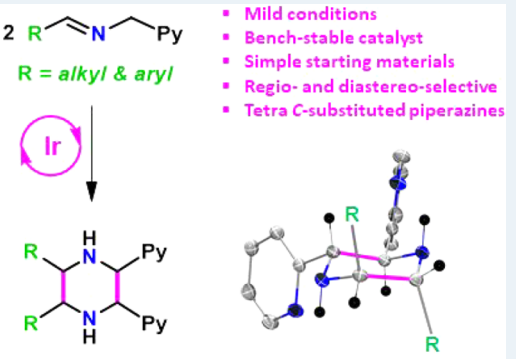
ABSTRACT: Piperazine rings are essential motifs frequently found in commercial drugs. However, synthetic methodologies are mainly limited to *N*-substituted piperazines, preventing structural diversity. Disclosed herein is a straightforward catalytic method for the synthesis of complex C-substituted piperazines based on an uncommon head-to-head coupling of easily prepared imines. This 100% atom-economic process allows the selective formation of a sole diastereoisomer, a broad substrate scope, and a good functional group tolerance employing a bench-stable iridium catalyst under mild reaction conditions. Key to the success is the addition of *N*-oxides to the reaction mixture, as they notably enhance the catalytic activity and selectivity.



KEYWORDS: *piperazines, iridium, homogeneous catalysis, [3 + 3]-cycloadditions, imines, trimethylamine N-oxide*

The piperazine ring is a key pharmacophore for a wide range of drugs, including those with antibiotic, antidepressant, anti-HIV, anticancer, antiviral, antimicrobial, and anxiolytic activities (some examples are shown in Figure 1).[1]

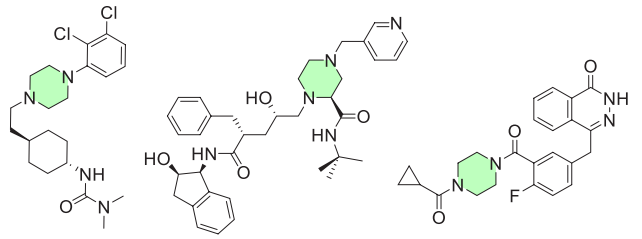


Figure 1. Selected examples of pharmaceuticals containing a piperazine motif.

Considerable efforts have been devoted to the development of synthetic routes yielding this privileged drug scaffold, which have traditionally focused on the reduction of diketopiperazines, the reductive amination of dicarbonyl compounds, and transition-metal-catalyzed cyclization reactions.[2] These methods often require multistep synthesis, as well as protecting and deprotecting steps.[3] More sustainable approaches include a "borrowing hydrogen" method, which uses 1,5-diols and primary amines, the synthesis of 2-substituted piperazines by an iridium photocatalyst,[4] and biocatalytic reductive aminations of 1,2-dicarbonyl and 1,2-diamine substrates, which yield piperazines in an atom-economical fashion.[5]

As for any drug, the individual architecture is crucial for the drug−target interactions and therefore directly impacts on the inherent properties and specific function of the resulting molecule.[1e] Moreover, the increase of molecular complexity and the number of stereogenic centers, also referred to as escaping from flatland, has been deemed key for the exploration of chemical space potentially, leading to unexplored molecular recognition with biological receptors within an active site.[6] These altered vectors can be advantageous, leading to chemical diversity and unique pharmaceutical activities.

An analysis of piperazine cores in pharmaceuticals reveals limited structural diversity, with most examples containing substituents on the N atoms, but limited examples of C-substituted piperazines.[1a,c,d] Whereas the functionalization of the nitrogen atoms is relatively straightforward, the post-synthetic functionalization of the carbon atoms can be extremely challenging.[7] Therefore, there is great interest in

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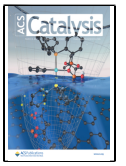
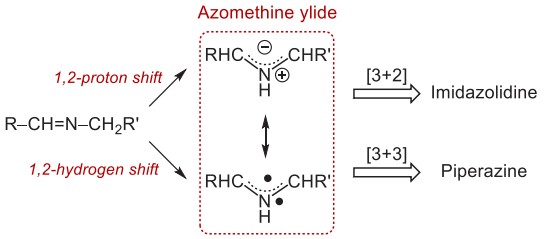


the development of new synthetic routes yielding carbon-substituted piperazines in a straightforward manner.[1b]

In this context, easily prepared imines featuring the "CH═N—CH_2" motif could be valuable synthons to C-substituted piperazines via the dimerization of the highly reactive azomethine ylide isomer (Scheme 1).

Scheme 1. Pathways for Azomethine Ylides from Imines, Zwitterion and Diradical Resonant Forms, and Possible Cycloaddition Reactions



Although the prevalent reaction mode for these intermediates is [3 + 2]-cycloadditions to imidazolidines,[8] selective [3 + 3]-cycloadditions to the piperazine ring have been observed at the stoichiometric level in a few instances. Pioneering works in organometallic chemistry involved complexes bearing deprotonated imines ([R—CH═N—CHR′]$^-$, smif-type ligands) of group 4 transition metals,[9] Fe,[10] Al,[11] and Zn,[12] which rendered binuclear complexes with a bridging dianionic piperazine. From these, free piperazines have been rarely isolated.[9b,11] More recently, an original combination of aluminum reagents under visible-light irradiation to form piperazines has been reported.[13] In this regard, we are not aware of previous examples of such [3 + 3]-cycloadditions at a catalytic level.

Herein, we showcase a powerful atom-economical method for the catalytic synthesis of C-substituted piperazines from formal [3 + 3]-cycloadditions of both aromatic and aliphatic imines. High yields and excellent regio- and diastereoselective control are achieved using [IrCl(cod)(PPh_3] (**5**, cod = 1,5-cyclooctadiene) as a catalyst under mild reaction conditions.

Initial studies started analyzing the response of [{Ir(μ-Cl)(cod)}$_2$] (**1**) toward Py^A—CH═N—CH_2Py^B (**2a**; Py = 2-pyridyl), which rendered the neutral complex [IrCl(cod)-(Py^A—CH═N—CH_2Py^B)] (**3**, Figure 2). A chelating coordination mode of the imine to iridium through the nitrogen atoms of the imine and Py^A is proposed in **3**, as found in related rhodium and iridium complexes.[14] A further addition of the imine to **3** gave [Ir(cod)(κ^3-*N*,*N*′,*N*″-HL1)]Cl ([**4**]Cl), where HL1 is an imidazolidine-type ligand (Figure 2). Most likely, the imidazolidine ring results from a 1,3-dipolar cycloaddition of the azomethine ylide moiety with the imine ([3 + 2]-cycloaddition), as described above.[8b]

To our delight, the addition of PPh_3 to **3** rendered the neutral compound [IrCl(cod)(PPh_3)] (**5**) and the piperazine **6a** (Figure 2). This reaction highlights the crucial role of PPh_3 in providing a divergent reaction pathway that controls the regioselectivity of the reaction to the six-membered piperazine instead of to the five-membered imidazolidine.

It is also worth noting the diastereoselectivity in the synthesis of **6a**, since only one diastereoisomer was quantitatively formed, as observed by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. Notice that the coupling of two imines renders four new C-stereocenters, so that three enantiomeric pairs and

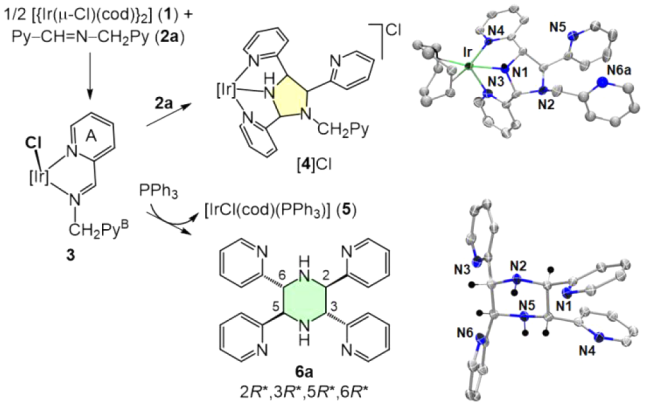


Figure 2. Reaction of [{Ir(μ-Cl)(cod)}$_2$] (**1**) with **2a** in C_6D_6 to give complex **3** and subsequent reactions either with a second equivalent of **2a** to give complex [**4**]Cl or with PPh_3 to yield [IrCl(cod)(PPh_3)] (**5**) and **6a**. [Ir] = Ir(cod). The molecular structures (ORTEP, ellipsoids set at 50% probability) of the cation [**4**]$^+$ and **6a** (2*R*,3*R*,5*R*,6*R*-enantiomer) are shown on the right. For selected bond distances and angles, see the Supporting Information.

three *meso* forms could be formed *a priori* from **2a**. The absolute configuration of isolated **6a** as the 2*R*,3*R*,5*R*,6*R* and 2*S*,3*S*,5*S*,6*S* enantiomeric pair (denoted as 2*R**,3*R**,5*R**,6*R**) was determined via X-ray crystallographic analysis (Figure 2). This configuration contrasts with that in the previous known examples, which systematically rendered the related isomer 2*R**,3*R**,5*S**,6*S**.

The reaction of **3** with PPh_3 was monitored by ^{1}H NMR spectroscopy. This reaction mixture cleanly evolved to the piperazine **6a** and complex **5** over 22 h, while the uncoordinated imine **2a** along with broad resonances for the cod peaks of **5** were initially observed. Accordingly, the direct reaction between equimolar amounts of [IrCl(cod)(PPh_3)] (**5**) and the imine **2a** yielded **6a** directly in a very good yield in 6 h (Figure S1).

At a catalytic level, using 2 mol% **5** in C_6D_6 at 25 °C, the reaction was found to be significantly more complicated. A mixture of imidazolidines (34%) along with only an 18% yield of the desired piperazine **6a** was obtained after 12 h of reaction (entry 1, Table 1 and Figure 3).

Table 1. Screening of the Reaction Conditions for the Catalytic Synthesis of 6a from 2a[a]

entry	solvent	additive	time (min)	conv. (%)[b]	select. (%)[b]
1	C_6D_6		744	52	11
2	C_6D_6	Na_2CO_3	512	90	77
3	C_6D_6	NEt_3	137	94	96
4	CD_2Cl_2	NEt_3	316	94	61
5	CD_3CN	NEt_3	187	95	72
6	C_6D_6	NEt_3-dist.	242	83	80
7	C_6D_6	$Me_3NO{\cdot}2H_2O$	93	97	94
8	CD_3CN	$Me_3NO{\cdot}2H_2O$	18	95	94
9	C_6D_6	C_6H_5NO	199	79	79
10	C_6D_6	TEMPO	246	68	76

[a]Reaction conditions: [IrCl(cod)(PPh_3)] (**5**, 0.0084 mmol), additive (0.084 mmol), and **2a** (0.42 mmol) in solvent (total volume = 0.5 mL) at 25 °C. [b]Selectivity to piperazine. Determined by ^{1}H NMR spectroscopy respect to an internal standard (toluene, 0.075 mmol).

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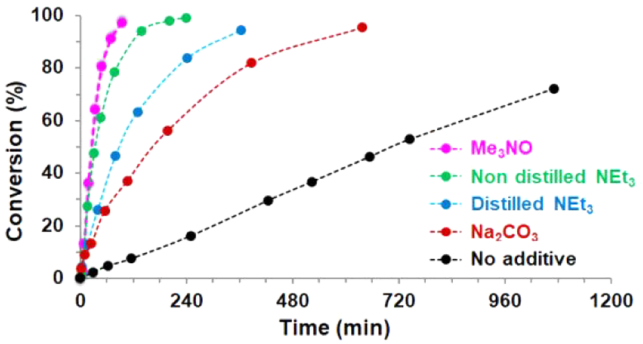


Figure 3. Plot of conversion (%) vs time (min) for the synthesis of piperazine **6a** catalyzed by **5** in C_6D_6 for Table 1 entries 1 (black), 2 (red), 3 (green), 6 (blue), and 7 (pink). Dashed lines are for visual aid.

Noticeably, the addition of a base such as Na_2CO_3 or NEt_3 resulted in a significant improvement in both regioselectivity and reaction times (entries 2 and 3, Table 1). Moreover, for the more effective NEt_3, small differences were observed in CD_3CN, while it was found to be slower in CD_2Cl_2 (entries 3−5, Table 1).

Surprisingly, it was found that the addition of NEt_3 purified by distillation resulted in a loss of the catalytic activity (entry 6, Table 1 and Figure 3). Analysis by mass spectroscopy of the unpurified NEt_3 indicated that it contained a small amount of triethylamine *N*-oxide (<5%). Therefore, the effect of *N*-oxides was analyzed by testing the catalysis in the presence of $Me_3NO{\cdot}2H_2O$, pyridine *N*-oxide (C_6H_5NO), and the radical *N*-oxide TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) (entries 7−10, respectively, Table 1).

Remarkably, the addition of 10 mol equiv Me_3NO in C_6D_6 considerably reduced the reaction time (entry 7). Moreover, the use of a polar solvent, such as CD_3CN, which increases the solubility of Me_3NO, resulted in 95% conversion in just 18 min (entry 8, Table 1). Through this methodology, the reaction was scaled-up to a gram scale, yielding **6a** as an off-white solid with a 94% isolated yield. In the same line, C_6H_5NO as well as TEMPO also accelerated the reaction, albeit to a lesser extent (entries 9 and 10, respectively, Table 1).

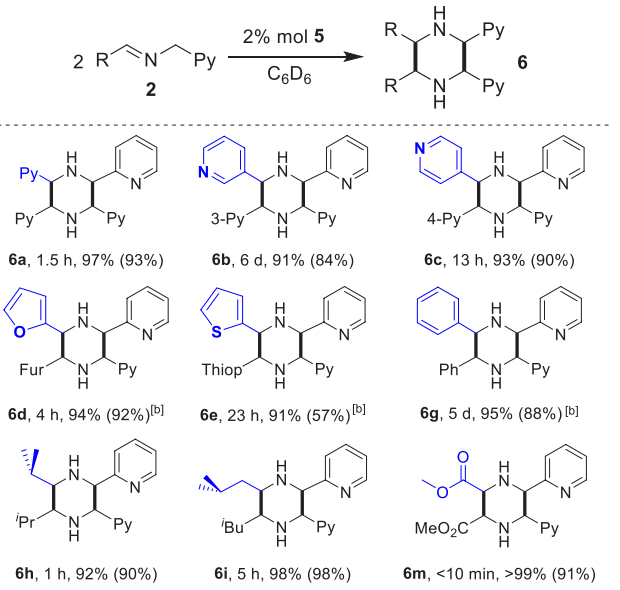
In a parallel experiment, the reaction between [IrCl(cod)-(PPh_3)] (**5**) and Me_3NO showed that **5** slowly converts to [IrCl(cod)($OPPh_3$)] with 18% conversion after 24 h. Therefore, it seems unlikely that this reaction has significant impact on is significantly impacted by the time scale of the catalysis. In addition, control experiments in the absence of **5** showed no conversion to piperazine with or without the presence of Me_3NO (Table S1).

The prominent role of Me_3NO could be derived from its expected ability to act as a hydrogen transfer reagent, as recently reported for related pyridine *N*-oxides,[15] which would provide a low-energy pathway to the azomethine ylide intermediate (Scheme 1, 1,2-hydrogen shift). In this regard, the reduced positive effect of bases and the more active *N*-oxide radical, TEMPO, could be related to the participation of the probably less reactive anionic [Py—CH═N—CHPy]$^-$ (^{Py2}smif) and radical [Py—CH═N—CHPy]$^\bullet$ intermediates, respectively.

The substrate scope was investigated under the experimental conditions outlined in entry 7 (Table 1). Although for Py—CH═N—CH_2Py the catalysis is faster in acetonitrile (entry 8, Table 1), for the rest of imines acetonitrile resulted in less selective reactions. Ultimately, the best compromise between conversion and selectivity was using C_6D_6 as the solvent.

As shown in Table 2, the reactions were found to be regioselective to the piperazine ring and diastereoselective to

Table 2. Scope of the Piperazine Synthesis.[a]



[a]For reaction conditions, see entry 7 in Table 1. The isolated yield is given in parentheses. [b]Reactions were performed at 60 °C.

the head-to-head 2*R**,3*R**,5*R**,6*R** isomer, as confirmed by NMR spectroscopy and X-ray diffraction studies on selected piperazines (**6a**, **6d**, and **6i**, see the Supporting Information).[16]

Moving the position of the N-atom on the pyridine bonded to the imine carbon using R—CH═N—CH_2Py (R = 3-pyridyl, 4-pyridyl) allowed the preparation of piperazines **6b** and **6c**, although it was associated in increased reaction times relative to **6a**. The same applies to imines featuring the heterocycles 2-furanyl and 2-tiophenyl, which rendered **6d** and **6e** in very good yields. In the same line, Ph—CH═N—CH_2Py (**2g**) produced **6g**, although the reaction was found to be very slow. Given the higher thermal stability of these imines (**2d**, **2e**, and **2g**), the reactions were performed at 60 °C. In the particular case of R = 2-pyrrolyl, only a trace amount of **6f** was obtained, which reveals the negative role of the acidic NH proton on the heterocycle.

Aliphatic imines, R—CH═N—CH_2Py (R = ^{i}Pr and ^{i}Bu), were found to convert in a facile manner into **6h** and **6i**, respectively, with relatively short reaction times at 25 °C. Meanwhile, the reaction with the more sterically encumbered aliphatic imine, Et_2CH−C═N−CH_2Py (**2j**), dramatically decreased the conversion and selectivity of the reaction, yielding a mixture of expected piperazine **6j** and imidazolidines.

Unlike aromatic imines, both aliphatic imines (**2h** and **2i**) converted to the corresponding piperazines in the absence of Me_3NO with comparable reaction times (Table S1). Such a difference could be attributed to the electron-donating nature (EDG) of the R group bonded to the imine carbon. Moreover, it was found that an activating group in the R′ position of the imine R—CH═N—CH_2R′ is key for the success of the catalysis. Indeed, no reaction occurred with Py—CH═N—

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$CHMe_2$ (**2k**) even after 4 days at rt. In the same line, the use of the imine Py—CH═N—CH_2Ph (**2l**) resulted in a considerable loss in the selectivity. A mixture of the piperazine **6l** and unidentified products (ratio 1:4) was obtained after 2 days at 60 °C (57% conversion), while the imine Py—CH═N—CH_2CO_2Me (**2m**) resulted in a noticeable increase of the reaction rate with a 99% conversion to **6m** in less than 10 min. These results agree with an enhanced catalytic activity with imines R—CH═N—CH_2R' featuring electron-donating groups (EDG) bonded to the CH and electron-withdrawing groups (EWG) bonded to the CH_2.

In conclusion, we have proved that C-substituted piperazines can be synthesized in a stereospecific and straightforward manner using an accessible iridium catalyst under mild reaction conditions. The developed method is very simple and scalable, as it only requires imines as the starting products. Furthermore, the unique diastereomer obtained has been previously unreported and indicates that a distinct reaction pathway is operating in this catalysis.

■ ASSOCIATED CONTENT

Data Availability Statement

Crystallographic data for piperazines **6a**, **6d**, **6i**, and for [**4**]Cl have been deposited in the Cambridge Crystallographic Data Centre (2218904−2218907).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c05895.

Experimental details; catalytic studies; and selected NMR spectra of the complexes, imines, and piperazines (PDF)

Crystallographic data for complex [**4**]Cl (CIF)

Crystallographic data for piperazine **6a** (CIF)

Crystallographic data for piperazine **6d** (CIF)

Crystallographic data for piperazine **6i** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) Due the change in the priorities of the substituents on the C atoms in piperazines **6h** and **6i**, the obtained diastereoisomers are in fact 2*S**,3*S**,5*R**,6*R**, but they correspond to the 2*R**,3*R**,5*R**,6*R** isomer of **6a**.

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