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C(sp^3)–H functionalization of *N*-protected dialkylpyrrole derivatives with azodicarboxylates

Jing Guo, †*[a] Maying Yan, †[a] Lei Xiao, [a] Jiajie Li, [a] Zheng-wang Qu, *[b] Stefan Grimme [b] and Douglas W. Stephan *[c]

A metal-free, catalytic route to the activation of C(sp^3)–H bonds in *N*-protected dialkylpyrroles to diazodicarboxylates is reported using HB(C$_6$F$_5$)$_2$ as the optimized catalyst. These reactions tolerate aryl and alkyl substituents on the pyrrole *N*-atom as well as variation in the azodicarboxylates giving rise to 41 examples. These reactions were also performed on a gram scale and conversion to the corresponding amino-esters is demonstrated. A DFT computation study reveals that the Lewis acid adduct of azodicarboxylates generates a Lewis acidic *N*-atom capable of hydride abstraction from dimethylpyrrole, ultimately effecting C(sp^3)–H functionalization.

Pyrrole is a privileged aromatic heterocycle that is found in chlorophyll, heme, vitamin B$_{12}$, and bile acids. Naturally occurring and synthetic molecules incorporating pyrrole units have been shown to exhibit a broad range of biological and pharmacological activities.[1] For example, over 20 synthetic pyrrole derivatives are commercially marketed drugs as such species exhibit anti-psychotic, anti-anxiolytic, anti-cancer, anti-bacterial, anti-fungal, anti-malarial, anti-inflammatory, and anti-hyperlipidemic behavior (Fig. 1a).[1a,1b]

Synthetic efforts to derivatize pyrroles have led to the development of a wide variety of transition metal catalyzed processes.[2] These protocols allow the incorporation of a wide range of functional groups, typically leading to substitution at N or at the C(sp^2) atoms at the C-2 or C-3 positions. These methods have been reviewed.[2b–e] Alternatively main group species are known to mediate the derivatization of *N*-protected pyrroles.[3] For example, Lewis acid mediated Friedel–Crafts methods readily provide substitution again at sp^2 carbons, where the steric demands of the *N*-protecting group can be used to direct substitution to either the C-2 or C-3 positions.[3]

In 2010, we showed that *N*-alkylpyrroles participate in frustrated Lewis pair (FLP) alkyne-addition reactions, leading to C–C bond formation at the C(sp^2) atoms at the C-3 position.[4] Several years later, in a seminal finding, Fontaine and coworkers[5] exploited intramolecular N/B FLPs to effect borylation of *N*-methylpyrrole, thiophene and furan derivatives, again at the C-2 or C-3 positions depending on the other substituents (Fig. 1b). Subsequently, Shi and coworkers used BBr$_3$ to direct C(sp^2)–H borylation of indoles at the C-7 or C-4 positions and other (hetero)arenes.[6] More recently, Tan *et al.* elegantly used chiral phosphoric acid catalysts to functionalize *N*-protected-pyrroles at the C-3 position, affording axially chiral arylpyrroles (Fig. 1b).[7]

In contemplating alternative strategies for the functionalization of pyrroles, we considered activation of the C(sp^3)–H bonds of substituents at the C-2 position. While the majority of the activation strategies for unactivated C(sp^3)–H bonds have been

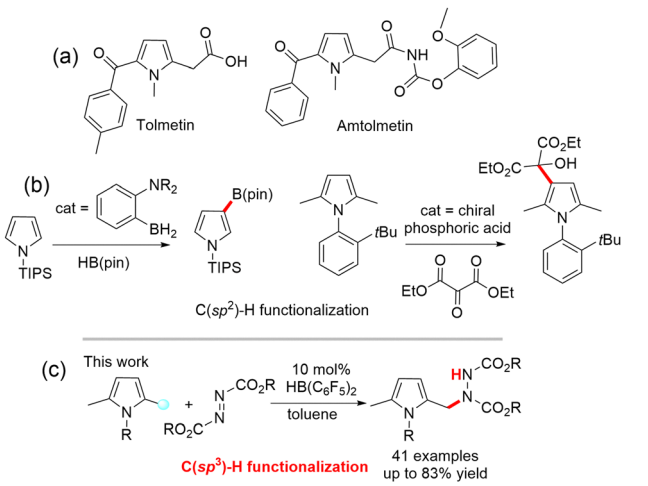


Fig. 1 (a) Representative pyrrole-derived drugs. (b) Metal free C(sp^2)–H functionalization of *N*-protected pyrroles. (c) This work – C(sp^3)–H functionalization of *N*-protected pyrroles with azodicarboxylates.

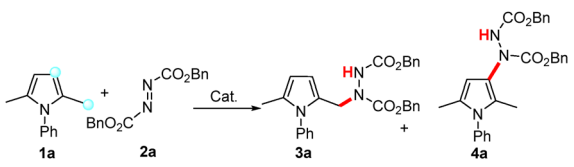
[a] *Institute of Drug Discovery Technology and Qian Xuesen Collaborative Research Center of Astrochemistry and Space Life Sciences, Ningbo University, Ningbo 315211, Zhejiang, China. E-mail: guojing@nbu.edu.cn*
[b] *Mulliken Center for Theoretical Chemistry, Clausius Institut für Physikalische und Theoretische Chemie, Rheinische Friedrich-Wilhelms-Universität Bonn, Beringstrasse 4, 53115 Bonn, Germany. E-mail: qu@thch.uni-bonn.de*
[c] *Department of Chemistry, University of Toronto, Toronto, 80 St. George Street, Ontario M5S 3H6, Canada. E-mail: douglas.stephan@utoronto.ca*
† J. Guo and M. Yan contributed equally to this work.

achieved using transition-metal catalysts,[8] we noted that boranes have been used as catalysts to promote C–C and C–heteroatom bond formation.[9] For example, Wang and coworkers achieved C(sp^3)–H alkylation of tertiary amines with electron-deficient olefins using $B(C_6F_5)_3$ as the catalyst.[10] In another recent breakthrough, Lin *et al.*[11] used frustrated radical pairs (FRPs) to functionalize the C(sp^3)–H bonds of various organic substrates, affording aminoxylated products. Nonetheless, to our knowledge, C(sp^3)–H bond activation of pyrrole derivatives is not known. Herein, we develop a protocol for the C(sp^3)–H bond functionalization of the methyl groups of *N*-protected methylpyrroles with azodicarboxylates using Piers' borane $HB(C_6F_5)_2$ as the catalyst (Fig. 1c).

Our investigation began with the reaction of *N*-phenylpyrrole **1a** and commercially available dibenzyl azodicarboxylate **2a** in toluene. In the presence of 10 mol% $Al(C_6F_5)_3$, this gave mixtures of C(sp^2)–H and C(sp^3)–H activation products, with poor regioselectivity at 60 °C (Table 1, entry 1). In the presence of $B(C_6F_5)_3$ and $HB(C_6F_5)_2$, the selectivity for the C(sp^3)–H functionalization product **3a** improved (Table 1, entries 2 and 3). Using $HB(C_6F_5)_2$ as the catalyst, product **3a** was obtained in 47% yield at 60 °C. Altering the reactant ratio of **1a**:**2a** to 1.5:1 afforded product **3a** in 61% yield with a 13% yield of the C(sp^2)–H functionalization product **4a** (Table 1, entries 3–6), while further variations of the solvent, temperature and catalyst loading did not increase the yield (Table 1, entries 7–12).

Using the optimized reaction conditions, the substrate scope for C(sp^3)–H functionalization of *N*-protected dialkylpyrroles with azodicarboxylates was examined. Firstly, the reactions of a series of *N*-arylpyrroles with **2a** in toluene were investigated. In the presence of 10 mol% $HB(C_6F_5)_2$, *para*-substituted *N*-arylpyrroles with electron-donating or electron-withdrawing substituents on the phenyl ring (Fig. 2, R = C_6H_5 **1a**, 4-FC_6H_4 **1b**, 4-ClC_6H_4 **1c**,

Table 1 Optimized reaction conditions for C–H functionalization



Entry[a]	Cat.	1a : 2a	Solvent	T (°C)	Yield (%) 3a[b]	Yield (%) 4a[b]
1	$Al(C_6F_5)_3$	1.0 : 1.5	Toluene	60	21	22
2	$B(C_6F_5)_3$	1.0 : 1.5	Toluene	60	43	6
3	$HB(C_6F_5)_2$	1.0 : 1.5	Toluene	60	47	6
4	$HB(C_6F_5)_2$	1.0 : 1.0	Toluene	60	47	12
5	$HB(C_6F_5)_2$	1.5 : 1.0	Toluene	60	61	13
6	$HB(C_6F_5)_2$	2.0 : 1.0	Toluene	60	55	13
7	$HB(C_6F_5)_2$	1.5 : 1.0	Benzene	60	57	14
8	$HB(C_6F_5)_2$	1.5 : 1.0	*p*-Xylene	60	52	10
9	$HB(C_6F_5)_2$	1.5 : 1.0	PhF	60	39	19
10	$HB(C_6F_5)_2$	1.5 : 1.0	Toluene	45	47	11
11	$HB(C_6F_5)_2$	1.5 : 1.0	Toluene	80	52	12
12[c]	$HB(C_6F_5)_2$	1.5 : 1.0	Toluene	60	23	26

[a] Unless otherwise noted, all reactions were performed using 10 mol% catalyst, **1a** and **2a** in solvent (2.0 mL) under argon for 12 h. [b] Isolated yield after chromatography. [c] 5 mol% catalyst.

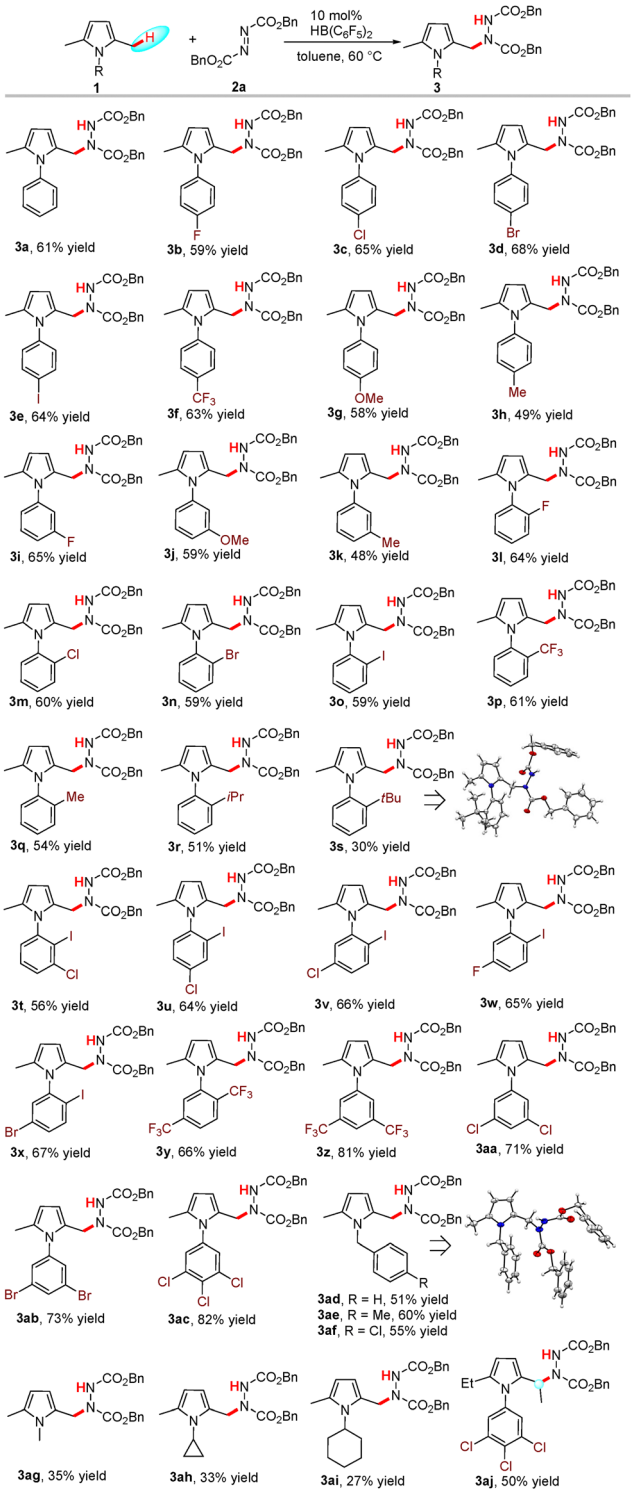


Fig. 2 Scope of *N*-protected dialkylpyrroles. Reaction conditions: a solution of **1** (0.3 mmol), dibenzyl azodicarboxylate **2a** (0.2 mmol) and $HB(C_6F_5)_2$ (10 mol%) in toluene (2.0 mL) was stirred at 60 °C for 1–2 h in argon.

4-BrC_6H_4 **1d**, 4-IC_6H_4 **1e**, 4-$CF_3C_6H_4$ **1f**, 4-$MeOC_6H_4$ **1g**, 4-MeC_6H_4 **1h**) reacted smoothly with **2a** to provide the corresponding products **3a–3h** in 49–68% yields. Similarly, *meta*-substituted *N*-arylpyrroles bearing differing functional groups (Fig. 2, R = 3-FC_6H_4 **1i**, 3-$MeOC_6H_4$ **1j**, 3-MeC_6H_4 **1k**) were tolerated, affording **3i–3k**

in 48–65% yields. *ortho*-Substituted *N*-arylpyrroles (Fig. 2, R = 2-FC_6H_4 **1l**, 2-ClC_6H_4 **1m**, 2-BrC_6H_4 **1n**, 2-IC_6H_4 **1o**, 2-$CF_3C_6H_4$ **1p**, 2-MeC_6H_4 **1q**, 2-*i*PrC_6H_4 **1r**, 2-*t*BuC_6H_4 **1s**) were also suitable substrates, affording the C(sp^3)–H functionalization products **3l–3s** in 30–64% yields. The identity of **3s** was confirmed by X-ray crystallography (see the SI).[12]

In addition, *N*-arylpyrroles with 2 or 3 substituents on the phenyl ring (Fig. 2, R = 2-I,3-ClC_6H_3 **1t**, 2-I,4-ClC_6H_3 **1u**, 2-I,5-ClC_6H_3 **1v**, 2-I,5-FC_6H_3 **1w**, 2-I,5-BrC_6H_3 **1x**, 2,5-$(CF_3)_2C_6H_3$ **1y**, 3,5-$(CF_3)_2C_6H_3$ **1z**, 3,5-$Cl_2C_6H_3$ **1aa**, 3,5-$Br_2C_6H_3$ **1ab**, 3,4,5-$Cl_3C_6H_2$ **1ac**) were also successfully converted to the C(sp^3)–H functionalized products **3t–3ac** in 56–82% yields. The reactions of *N*-benzylpyrroles (Fig. 2, R = CH_2Ph **1ad**, $CH_2C_6H_4Me$ **1ae**, $CH_2C_6H_4Cl$ **1af**) provided products **3ad–3af** in 51–60% yields. The nature of **3ad** was also confirmed by X-ray analysis (see the SI).[12] Moreover, alkylpyrroles (Fig. 2, R = Me **1ag**, C_3H_5 **1ah**, C_6H_{11} **1ai**) also reacted with **2a**, giving the products **3ag–3ai**, albeit in somewhat reduced yields of 27–35%. Furthermore, changing the pyrrole substituents to Et groups, as in **1aj**, afforded **3aj** in 50% yield, while the reaction of the dissymmetric pyrrole 2-Me-5-Ph-*N*-($C_6H_2Cl_3$)-pyrrole **1ak** with **2a** gave the C(sp^2)–H amination product **4ak** in 55% yield (see the SI).

Efforts to identify by-products were undertaken. Even on doubling the reaction scale for all reactions, most by-products were not unambiguously identifiable although the C(sp^2)–H amination products **4ah** and **4ai** were observed in 10 and 11% yields, respectively, while the double C(sp^2)–H amination product **4ag′** was observed in 9% yield (see the SI).

The reaction also tolerated variations in the azodicarboxylates. Thus, the reaction of the commercially available $(RO_2CN)_2$ (Fig. 3, R = $CH_2C_6H_4Cl$ **2b**, Et **2c**, *i*Pr **2d**) with **1ac** proceeded smoothly to give products **3ak–3am** in 43–83% yields. In contrast, the use of **2e** (R = *t*Bu) gave only a 19% yield of **3an** (Fig. 3). We note that this diazo-species is known to react with boranes to liberate CO_2 and isobutylene.[13] Notably, 4-phenyl-1,2,4-triazoline-3,5-dione **2f** also reacted smoothly with **1ac**, affording the desired product **3ao** in 40% yield.

The scalability of this protocol to gram-scale reactions was demonstrated. Thus, using over 2 grams of **1ac** with **2a** in the presence of 10 mol% $HB(C_6F_5)_2$ afforded 2.35 g of **3ac** in an overall yield of 82% (Fig. 4). In addition, **3ac** was reacted with bromoacetate and Cs_2CO_3 using the method of Magnus *et al.*,[14] affording $C_4H_2Me(CH_2NH(CO_2CH_2Ph)N(C_6H_2Cl_3)$ **5** in 70% yield (Fig. 4). This carbamate ester was characterized by X-ray crystallography (see the SI).[12]

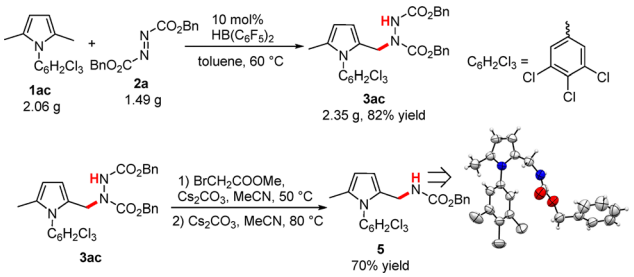


Fig. 4 Scale-up synthesis and synthetic transformation.

The mechanism of these reactions was established *via* a computational study using density functional theory (DFT) computations at the PW6B95-D3/def2-QZVP + COSMO-RS//TPSS-D3/def2-TZVP + COSMO level of theory.[15] As $B(C_6F_5)_3$ and $HB(C_6H_5)_2$ showed similar reactivity, $B(C_6F_5)_3$ was used in the calculations to avoid the complexity associated with the dimerization equilibrium of Piers' borane in solution. The initial interaction of $B(C_6F_5)_3$ with the carbonyl fragment of azodicarboxylate **2c** enhances the Lewis acidity of the remote *N*-atom, allowing it to abstract hydride from methylpyrrole **1a** over a free energy barrier of 22.5 kcal mol^{-1} (**TS1**). This generates the transient ion pair $\mathbf{1a}^+$ and $\mathbf{2cBH}^-$ (Fig. 5), which reacts exothermically to form a new C–N bond. The release of borane is slightly endergonic, allowing the catalytic reaction to continue, consistent with both experimental conditions and the improved catalysis for $(C_6F_5)_2BH$, where the slightly reduced Lewis acidity presumably accelerates the Lewis acid release. Regarding the role of the N-Lewis acid, we note that such species have been pioneered by Gandelman,[16] although we[17] and others[18] have described related diazo-derived Lewis acid systems.

In conclusion, we have reported a metal-free, catalytic and scalable protocol for the functionalization of C(sp^3)–H bonds in

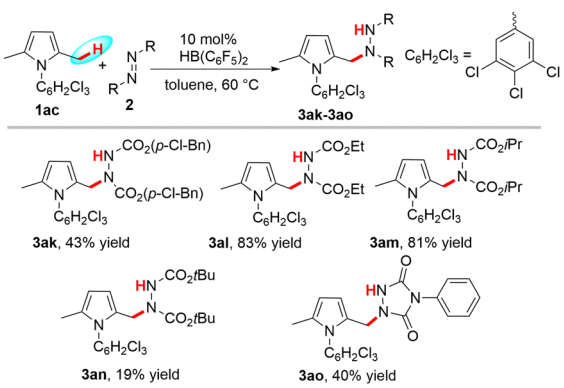


Fig. 3 Scope of azodicarboxylates. Reaction conditions: a solution of **1ac** (0.3 mmol), dibenzyl azodicarboxylate **2** (0.2 mmol) and $HB(C_6F_5)_2$ (10 mol%) in toluene (2.0 mL) was stirred at 60 °C for 1–2 h in argon.

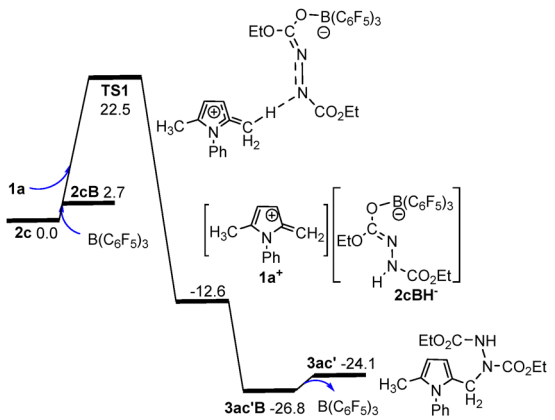


Fig. 5 DFT computed mechanism (in kcal mol^{-1}, at 298 K and 1 M concentration) for C(sp^3)–H functionalization of *N*-Ph-dimethylpyrrole to azodicarboxylates.

N-protected dimethylpyrroles with azodicarboxylates. The resulting diazo-pyrrole derivatives can be converted to the corresponding amino-esters. A mechanistic study showed that the Lewis acid adduct of the azodicarboxylate generates a Lewis acidic *N*-atom capable of hydride abstraction from the C(sp^3) carbon on the pyrrole. We are continuing to study metal-free avenues for C–H functionalization and Lewis acid applications in organic synthesis.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support this study are available in the SI of this article.

Experimental and spectral data are available as SI See DOI: **https://doi.org/10.1039/d5cc03254g**

3s: CCDC 2434837; **3ad:** CCDC 2434838 and **5:** CCDC 2434839 contain the supplementary crystallographic data for this paper.[19–21]

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