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Letter

Cross-Dehydrogenative N–N Coupling of Aromatic and Aliphatic Methoxyamides with Benzotriazoles

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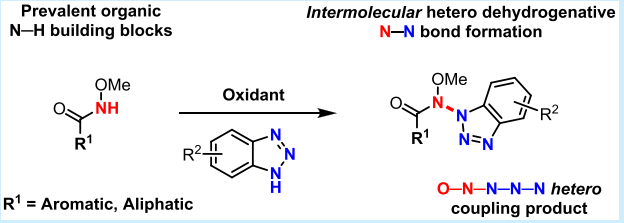
ABSTRACT: Nitrogen–nitrogen bond containing motifs are ubiquitous in bioactive compounds and organic materials. However, intermolecular hetero-selective N–H/N–H oxidative coupling reactions remain very challenging and largely unexplored. Here, we report an unprecedented, simple and hetero-selective cross-dehydrogenative N–N coupling of amides and benzotriazoles, utilizing only a hypervalent iodine species as the terminal oxidant. The scope and mechanistic investigations are discussed.



Nitrogen–nitrogen bonds represent an important functional group in numerous pharmaceuticals,[1] natural products,[2] organic materials[3] and dyes[4] (Figure 1). However,

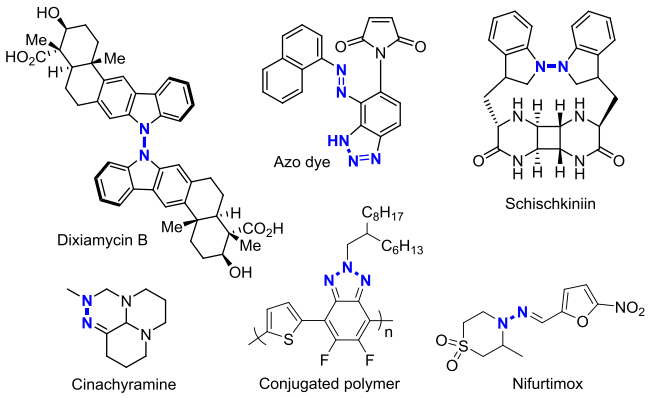


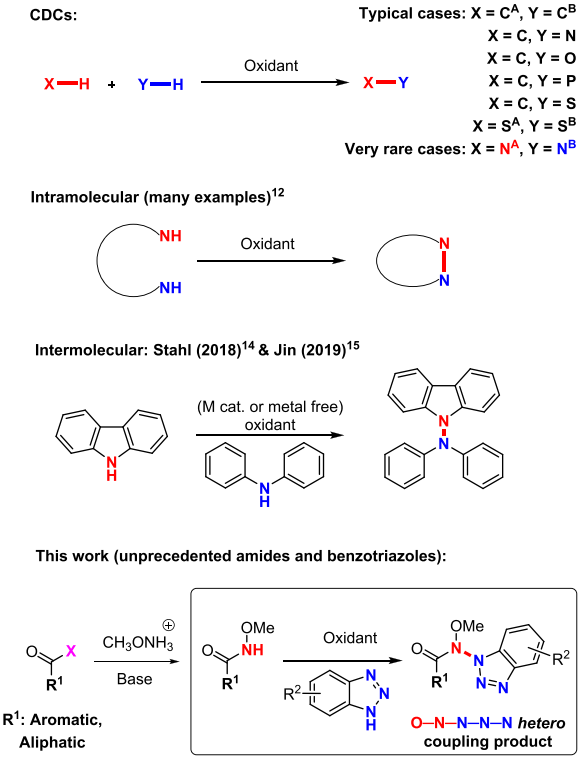
Figure 1. Important N–N bond containing compounds.

their construction typically relies on diazotization methods or the use of electrophilic nitrogen sources (e.g., oximes, hydrazones, nitriles, azides, and nitroso or other N-functionalized reagents).[5] Although these methods are effective, the development of direct dehydrogenative N–N bond forming strategies remains very scarce.

Meanwhile, cross-dehydrogenative coupling (CDC) reactions have become an increasingly popular strategy due to their step and atom economic nature (Scheme 1).[6] Furthermore, they have been extensively utilized to generate unique C–C,[6] C–N,[7] C–O,[8] C–P,[9] C–S,[10] and hetero S^A–S^B bonds[11] with high selectivity, while surpassing the need of preactivated substrates. Yet, intermolecular cross-dehydrogenative N–N coupling reactions remain heavily unexplored.

In the past, dehydrogenative N–N coupling reactions have been typically utilized for the construction of intramolecular

Scheme 1. N–N Bond Forming CDCs



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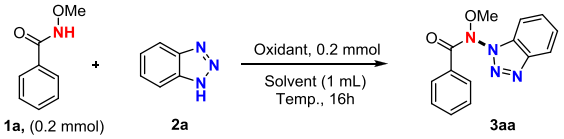
N–N bonds[12] or N–N homocoupled products.[13] However, intermolecular dehydrogenative hetero N–N coupling reactions remain elusive. To the best of our knowledge, the only methods that demonstrate some intermolecular hetero-cross-dehydrogenative N–N coupling were reported by Stahl and independently by Jin (2018 and 2019, Scheme 1).[14,15] These methods however are strictly limited to carbazoles and diarylamines, thereby leaving the N–N dehydrogenative bond forming toolbox almost empty. Hence, there remains a great demand for novel dehydrogenative reactions that allow hetero N–H/N–H coupling of other ubiquitous nitrogen motifs, besides carbazoles and diarylamines. We present here the first highly selective and efficient dehydrogenative cross-coupling of structurally and biologically relevant amides[16] and benzotriazoles,[17] utilizing very simple and mild reaction conditions.

Our investigation began with *N*-methoxybenzamide **1a** and benzotriazole **2a** as model substrates. Previous literature conditions[14,15] utilizing either Cu/O_2 or KI/KIO_4 did not deliver the desired product **3aa** (Table 1, entries 1 and 2).

Table 1. Reaction Optimization[a]



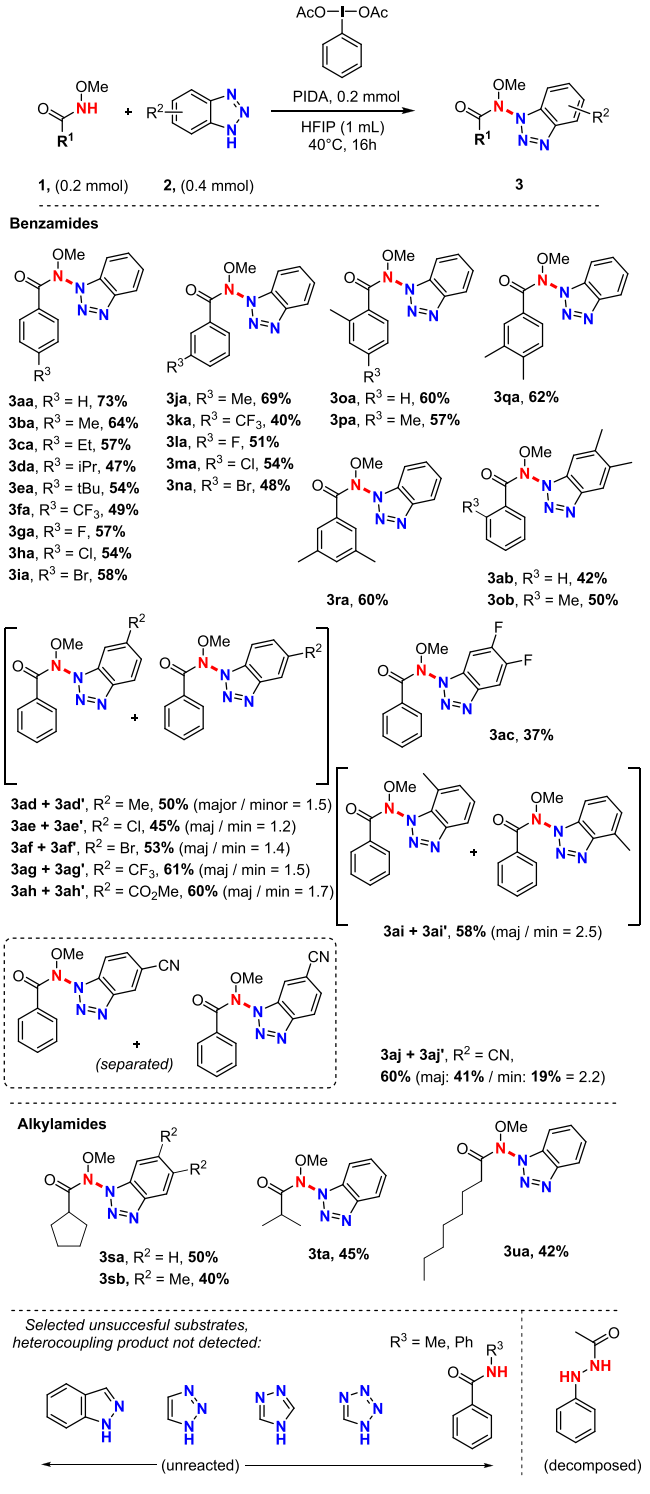
	Oxidant	Equiv (1a/2a/Ox.)	Solvent (Temp, °C)	Yield (%)[a]
1	O_2[b]	1:1.5:–	DMF (100)	0
2	KIO_4[c]	1:1:1.5	HFIP (40)	0
3	PIDA	1:1:1	HFIP (40)	51
4	PIDA[b]	1:2:1	HFIP (40)	49
5	PIDA[c]	1:2:1	HFIP (40)	62
6	PIDA	1:1:2	HFIP (40)	45
7	PIDA	1:1.5:2	HFIP (40)	65
8	PIDA	1:3:2	HFIP (40)	65
9	**PIDA**	**1:2:1**	**HFIP (40)**	**73**
10	PIFA	1:2:1	HFIP (40)	41
11	IBX	1:2:1	HFIP (40)	0
12	HTIB	1:2:1	HFIP (40)	54
13	PIDA	1:2:1	TFE (40)	58
14	PIDA	1:2:1	TCE (40)	54
15	PIDA	1:2:1	CH_3CN (40)	50
16	PIDA	1:2:1	HFIP (50)	60
17	PIDA	1:2:1	HFIP (60)	58
18	PIDA	1:2:1	HFIP (60)[d]	68

[a]Isolated yields. [b]Reaction with CuBr(DMS).[14] [c]Reaction with KI. [d]Reaction for 6 h.

Instead, the starting materials remained completely unreacted, showing no conversion. Next, hypervalent iodine oxidants were tested. To our delight, a highly selective N–N cross-coupling was observed immediately with (diacetoxyiodo)benzene[18] (benzamide/triazole/PIDA = 1:1:1, entry 3), affording the N–N hetero-coupling product in 51% yield. In the latter reaction, the unreacted benzotriazole starting material was recovered in 42% yield, indicating that no appreciable side products (<7%) were formed during the process from the triazole.

In contrast, only a trace of benzamide starting material could be detected, suggesting a competing oxidative decomposition pathway which is moreover probably not homo-coupling. Indeed, in none of these reactions (Table 1, Schemes 2, 3 and 4) were any homo-coupling products ever detected. If they are present, it must therefore be in very small amounts. Increasing the ratio of benzotriazole to 2 equiv (1:2:1, entry 9) resulted in 73% of N–N cross coupled product **3aa** (entry 9). Other hypervalent iodine oxidants either rendered the product in lower yields (entries 10 and 12) or not at all (entry 11). Out of a few selected solvents (entries 8, 13–15), hexafluoroisopro-

Scheme 2. Cross-Dehydrogenative N–N Coupling of Methoxyamides with Benzotriazoles, Isolated Yields



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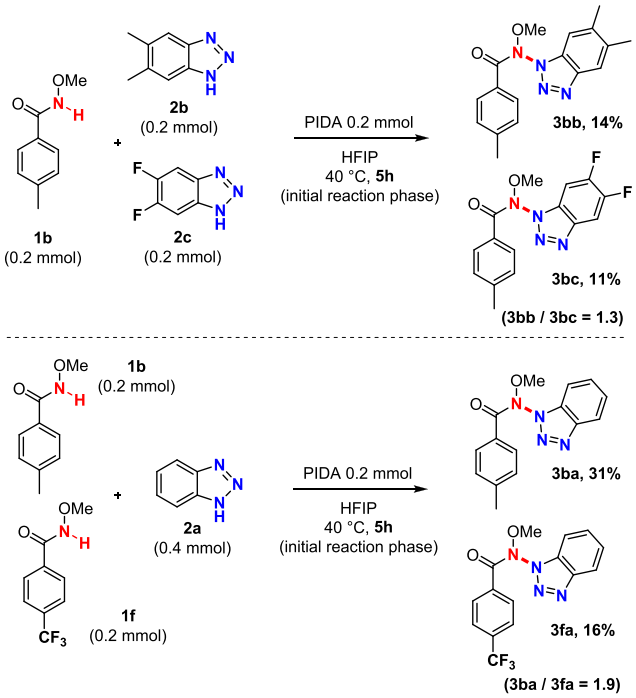
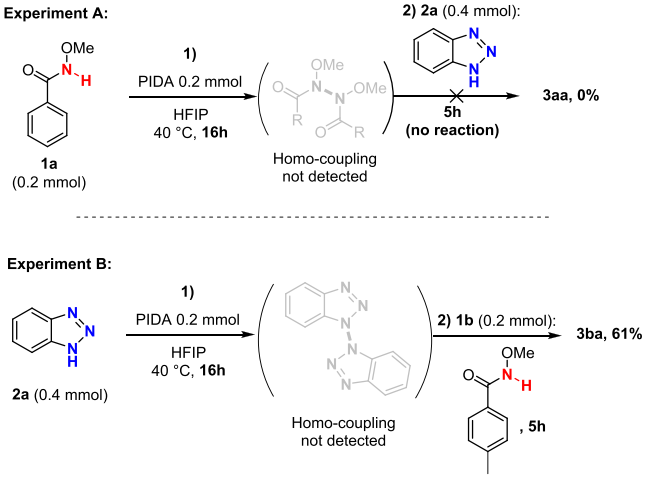
Scheme 3. Competition Experiments



Scheme 4. Sequential Addition Experiments



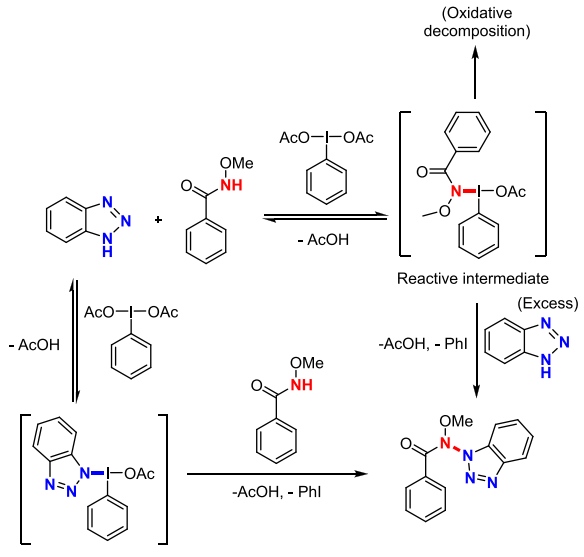
panol (HFIP) provided the best results. With the optimized conditions in hand, the substrate scope of the reaction was then investigated. Several *N*-methoxyamides and benzotriazoles were tested, which showed remarkable functional group tolerance (Scheme 2). For example, alkyl, halide, CF_3, cyano, and carboxyl ester groups on both the amide and triazole gave their corresponding N−N cross-coupled products in good yields. When monosubstituted benzotriazoles are engaged, isomeric mixtures of products are typically obtained due to similarly reacting and no longer symmetrical N-centers. For example, benzotriazole-6-carbonitrile led to an encouraging 1 to 2.2 mixture (**3ak** and **3ak′**), whereas 7-methyl-benzotriazole led to a 1 to 2.5 mixture of regioisomers (**3aj** and **3aj′**). Unfortunately, none of the regioisomers could be assigned at this stage due to inconclusive NOESY characterization. Importantly, however, ubiquitous aliphatic amides were well accommodated in the reaction (**3sa**, **3sb**, **3ta**, **3ua**), thus significantly enhancing the scope of the herein described method.

We then carried out some key mechanistic experiments. Because it was observed that electron-poor benzotriazoles (e.g., dihalides and tetrahalides) resulted in lower conversion to the desired heterocoupling product, such as for **3ac**, we ran a couple of competition experiments in order to probe the relative philicity of each coupling partner in this reaction (Scheme 3). From the latter it can be concluded that both amides and benzotriazoles convert faster to the desired N−N coupling product if they are more electron rich. There thus does not exist any clear electrophile−nucleophile relationship between the two coupling partners during the rate determining step(s). Next, the reaction was also attempted by replacing *N*-methoxy benzamide with *N*-methyl benzamide or *N*-phenyl benzamide. No conversion occurred however in such cases, suggesting that the *N*-methoxy group is essential and plays an enabling role in this reaction. Furthermore, the fact that only hypervalent iodine compounds competently operate as oxidants in this reaction, in contrast to $K_2S_2O_8$, Ag_2O, chloramine-T, DTBP, or O_2, suggests the structural involvement of the oxidant.

In order to elucidate the sequence of events that lead to the N−N hetero-coupling product, we then performed sequential addition experiments (Scheme 4). We thus initiated the reaction while omitting either the benzotriazole (Experiment A) or alternatively the amide (Experiment B). After 16 h, the second substrate was added. Remarkably, no N−N hetero-coupling product could be detected in the first scenario (Experiment A), while a good yield of product **3ba** was obtained in the second scenario (Experiment B, Scheme 4). It can therefore be concluded that the amide substrate irreversibly decays in the presence of PIDA, while the benzotriazole survives. The oxidative decay byproducts could not be identified at this stage. This nevertheless suggests a competing N−H activation scenario, wherein only the activation of the benzotriazole would be reversible under reaction conditions, justifying the need for an excess. These mechanistic elements are summarized in Scheme 5.

Next, the reaction could be scaled up with only minor adjustments (reaction temperature from 40 to 60 °C, Scheme

Scheme 5. Proposed Reaction Mechanism



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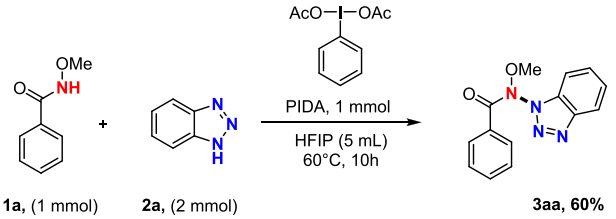
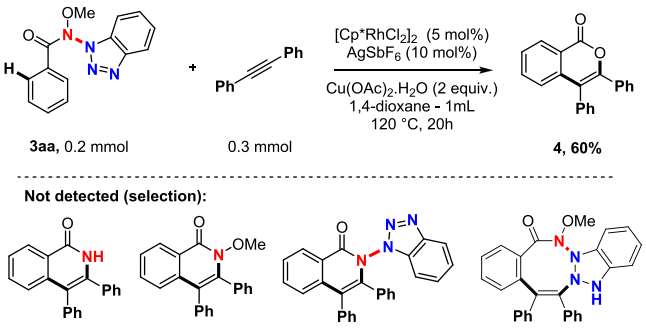
6) to afford an encouraging yield of 60%, which illustrates the synthetic utility of this novel transformation.

Scheme 6. Scale-up Experiment



Finally, in order to illustrate some potential future application of this completely novel O−N−N−N−N functional group, we investigated its directing group ability in a simple RhCp* catalyzed C−H bond activation coupling experiment. Thus, under typical Rh catalyzed C−H bond activation conditions,[19] we coupled **3aa** to diphenylacetylene in good yield (product **4**, Scheme 7). To our surprise, however,

Scheme 7. Directing Group Ability in a C−H Bond Activation Coupling Reaction



none of the four nitrogen atoms were found in the product, indicating that this new O−N−N−N−N functionality acts as an efficient leaving group in the context of metal catalyzed C−H bond activation. The oxygen atom that has replaced it in the isocoumarin backbone **4** likely comes from water traces in the solvent or from the hydrated Cu(II) salt, which serves as the oxidant in this reaction.

In conclusion, we developed an unprecedented cross-dehydrogenative N−N bond coupling between important *N*-methoxyamides and benzotriazoles. This metal-free method is mild, robust, and highly selective. Given the rich history concerning amides, benzotriazoles[17] and PIDA,[18,20] and the lack of efficient hetero N−N bond forming reactions, this transformation represents a significant milestone in the direction of widely applicable intermolecular N−H/N−H oxidative cross-couplings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01034.

Experimental procedures, characterization and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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