Synthetic Methods

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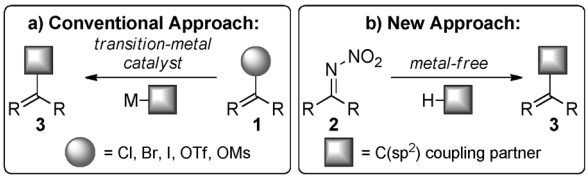
Nitrimines as Reagents for Metal-Free Formal C(sp^2)–C(sp^2) Cross-Coupling Reactions**

*Veronica V. Angeles-Dunham, David M. Nickerson, Devin M. Ray, and Anita E. Mattson**

Abstract: *Nitrimines are employed as powerful reagents for metal-free formal C(sp^2)–C(sp^2) cross-coupling reactions. The new chemical process is tolerant of a wide array of nitrimine and heterocyclic coupling partners giving rise to the corresponding di- or trisubstituted alkenes, typically in high yield and with high stereoselectivity. This method is ideal for the metal-free construction of heterocycle-containing drug targets, such as phenprocoumon.*

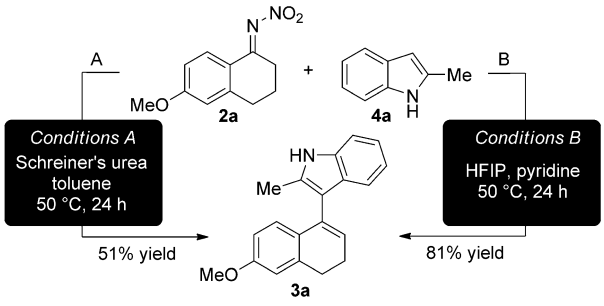
Carbon–carbon cross-coupling reactions are impressive tools for the reliable and effective assembly of functional target molecules.[1] Transition-metal-catalyzed C(sp^2)–C(sp^2) coupling reactions are one family of remarkably useful reactions. These processes often employ vinyl and aryl halides, triflates, or mesylates (**1**) as starting materials, likely because of the proposed mechanistic requirement of the metal catalyst to undergo oxidative addition into the carbon–halide or pseudohalide bond (Scheme 1 a). Given our goal to discover metal-free approaches to reactions that typically rely on transition-metal catalysis,[2] we set out to investigate functionalities that would accommodate the assembly of useful C(sp^2)–C(sp^2) bonds without the requirement of a metal catalyst. The development of metal-free formal C(sp^2)–C(sp^2) chemical reactions would provide the following benefits: a) the advancement of reaction pathways complementary to transition-metal-catalyzed coupling reactions and b) alleviation of the reliance of cross-coupling reactions on rare, expensive and/or toxic transition-metal catalysts. These potential advantages prompted us to study nitrimines (**2**) as innovative reagents for cross-coupling reactions (Scheme 1 b). Herein, we report our successful use of nitrimines as reagents in metal-free formal C(sp^2)–C(sp^2) cross-coupling reactions.



Scheme 1. Nitrimines as alternatives to conventional reagents for metal-free formal C(sp^2)–C(sp^2) cross-coupling chemical reactions. OTf = trifluoromethanesulfonate. OMs = mesylate.

Nitrimines are fascinating functional groups that are rarely employed in synthetic chemistry.[3] Nitrimines are easily prepared, benefit from high electrophilicity, and typically produce relatively harmless byproducts, such as nitrous oxide and water. Historically, nitrimines have been employed in the preparation of hindered ketones and aldehydes from oximes.[4] Beyond this traditional reactivity pattern, there are scattered reports of nitrimines undergoing additional reactions, such as Knoevenagel condensation,[5] reductions,[6] rearrangements,[7] and cycloadditions.[8] As we became interested in exploiting the attractive reactivity of nitrimines in innovative, metal-free procedures, we were inspired by their nitrogen-based nucleophilic exchange reactions.[9] To this end, we demonstrated that urea-activated nitrimines provide access to an impressive array of sterically-encumbered enamines.[10] Our success with nitrimine-based C–N cross-coupling reactions prompted us to question the potential utility of nitrimines in more challenging metal-free C–C cross-coupling reactions. To our knowledge, the unique reactivity of nitrimines had not been taken advantage of for formal C(sp^2)–C(sp^2) coupling reactions prior to our investigations.

Our studies were initiated with the reaction of the nitrimine of 6-methoxytetralone **2a** and 2-methylindole (**4a**) to generate the cross-coupled product **3a** (Scheme 2). Two distinct sets of reaction conditions emerged from our optimization of this process,[11] each with their own advantages. Under conditions A, 20 mol% of Schreiner's urea



Scheme 2. C(sp^2)–C(sp^2) cross-coupling reactions between nitrimine **2a** and reagent **4a**.

[*] V. V. Angeles-Dunham, Dr. D. M. Nickerson, D. M. Ray, Prof. Dr. A. E. Mattson
Department of Chemistry and Biochemistry
The Ohio State University
100 W. 18th Ave., Columbus, OH 43210 (USA)
E-mail: mattson@chemistry.ohio-state.edu
Homepage: http://mattson.group.chemistry.ohio-state.edu/

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(1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea)[12] was found to catalyze the addition of **4a** to **2a** to yield a modest amount of **3a** after 24 hours in toluene at 50 °C.[13] Alternatively, when hexafluoroisopropanol (HFIP) was employed as solvent (conditions B), no additional catalyst was necessary and **3a** was isolated in high yield (81 %) after 24 hours at 50 °C in the presence of a pyridine additive.[11]

After confirmation of the feasibility of metal-free nitrimine-based carbon–carbon cross-coupling reactions, we became interested in exploring their potential as reagents for the preparation of active pharmaceutical ingredients. Indole-, pyrrole-, and coumarin-containing therapeutic agents served as the inspiration for our studies. For example, RU24969,[14] phenprocoumon, and tipranavir are attractive medicinal targets which may benefit from nitrimine cross-coupling chemistry (Figure 1). With these targets in mind, the scope of reactions between various nitrimine electrophiles and coupling partners was explored.

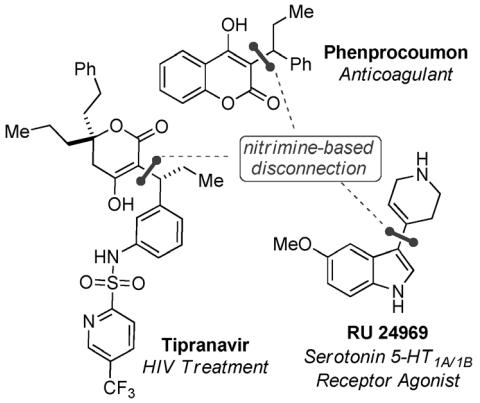
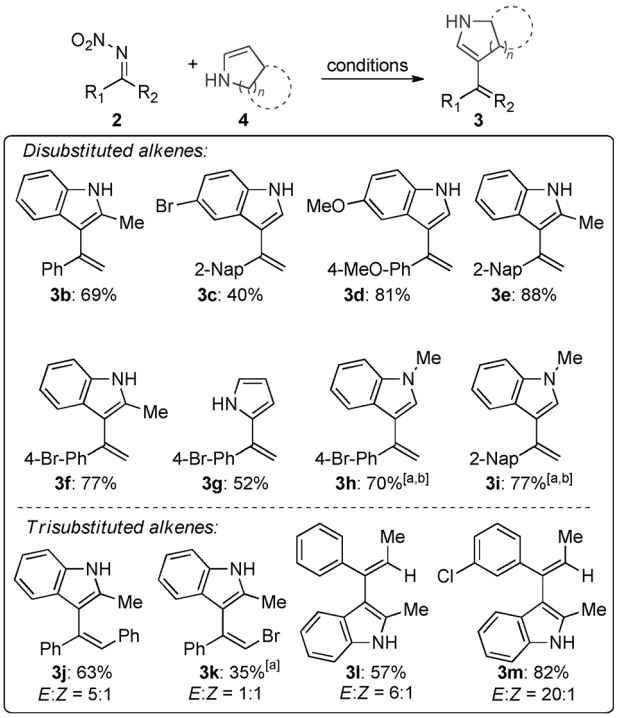


Figure 1. Potential nitrimine-based disconnections in drug discovery.

Reactions between less sterically encumbered nitrimines and nucleophiles were most efficient in pyridine at 50 °C in the absence of HFIP (Scheme 3). A variety of acetophenone-derived nitrimines and nucleophilic nitrogen heterocycles, including indoles and pyrrole, were well tolerated in the process. For instance, 2-methylindole and 5-bromoindole coupled to acetophenone-derived nitrimines to generate **3b** and **3c** in moderate yields (69 % and 40 %, respectively). Both electron-rich and electron-poor nitrimines operated smoothly, enabling the preparation of **3d**–**3g** in high yields. *N*-methylindole also proved to be a useful nucleophile, as good yields of terminal alkenes **3h** and **3i** were obtained. Interestingly, *N*-methylindole was a more efficient reagent when using conditions A (that is, the urea catalyst in toluene). In addition to enabling synthetic access to terminal, disubstituted alkenes, this process is useful for the direct construction of sterically hindered trisubstituted olefins (**3j**–**3m**). The reaction of 2-methylindole and the nitrimine derived from deoxybenzoin gave rise to **3j** in good yield as a 5:1 ratio of *E*:*Z* alkene isomers. Vinyl bromide **3k** was prepared in moderate yield as a 1:1 mixture of stereoisomers. The reaction of 2-methylindole with the nitrimine derived from propiophenone gave rise to the formation of **3l** which was isolated in



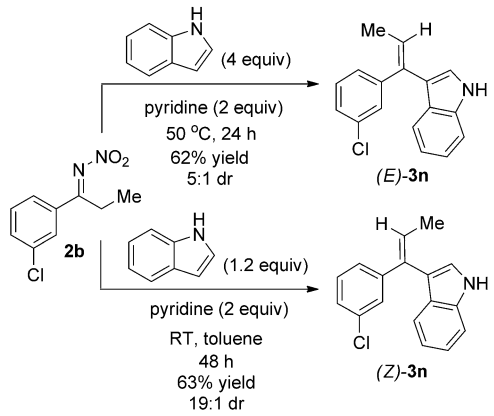
Scheme 3. Selected nitrogen heterocycles and nitrimine reagents tolerated in cross-coupling reactions. Unless otherwise noted, reactions were conducted using conditions B: pyridine, 50 °C, 24 hours. Yields determined from product isolated using silica gel chromatography. [a] Reactions conducted using conditions A: toluene, Schreiner's urea, 50 °C, 24 hours. See the Supporting Information for experimental details. [b] 48 hours reaction time. Nap = naphthalene.

57 % yield as a 6:1 mixture of *E*:*Z* isomers, and the product **3m** was prepared in high yield with excellent diastereocontrol over alkene geometry.

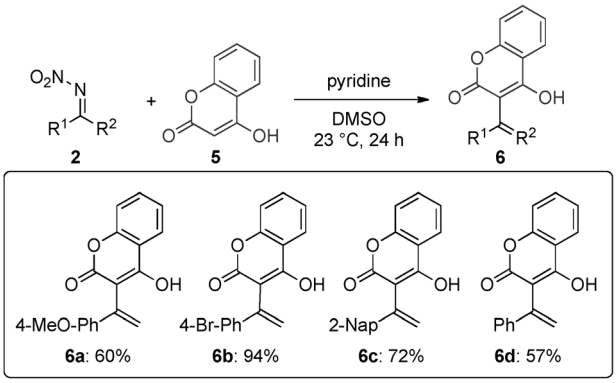
We were delighted to find that strategic monitoring of the reaction conditions enabled excellent control over the final alkene geometry of highly substituted alkenes (Scheme 4). At slightly increased reaction temperatures (50 °C) and using an excess of indole, the majority of nitrimine **2b** was converted into the *E* stereoisomer of **3n**. On the other hand, when the reaction was conducted at 23 °C in toluene with 1.2 equivalents of indole, the *Z* stereoisomer of **3n** was prepared in 63 % yield.

In addition to nitrogen-based heterocycles, hydroxycoumarins participated in cross-coupling reactions with a variety of nitrimines to afford products (**6a**–**d**) in high yields using DMSO (dimethylsulfoxide) as solvent (Scheme 5). For instance, the reaction of hydroxycoumarin with nitrimines derived from 4-methoxyacetophenone and 4-bromoacetophenone gave rise to the formation of disubstituted alkenes **6a** and **6b** in 60 % and 94 % yields, respectively. Alkene **6c** was isolated in 72 % yield, and the reaction of the acetophenone-derived nitrimine and **5** gave rise to the formation of product **6d** in a modest 57 % yield.

Pleased with the array of products (**3a**–**m** and **6a**–**d**) accessible using our metal-free nitrimine coupling procedure, we turned our attention toward applying the new method in the synthesis of the active pharmaceutical ingredient



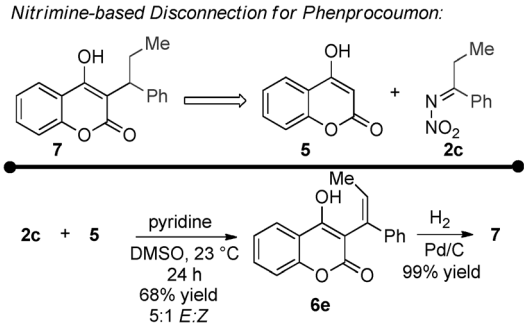
Scheme 4. Effect of varying the reaction conditions on the geometry of alkene products in nitrimine-based cross-coupling reactions. dr = diastereomeric ratio.



Scheme 5. Selected examples of cross-coupling reactions between 4-hydroxycoumarin and nitrimine electrophiles.

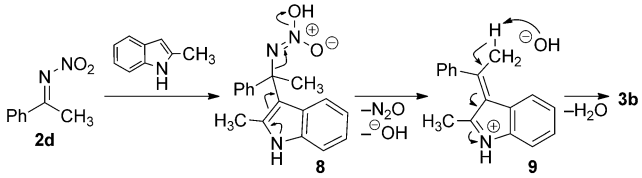
phenprocoumon (Scheme 6). The reaction of 4-hydroxycoumarin (**5**) and nitrimine **2c** afforded the desired trisubstituted alkene intermediate **6e** in 68% yield as a 5:1 mixture of *E*:*Z* isomers. The reduction of **6e** was easily achieved in quantitative yield under standard reaction conditions to afford desired product **7**.

A working hypothesis for the reaction pathway involved in formal $C(sp^2)$–$C(sp^2)$ cross-coupling reactions between selected heterocycles and nitrimine electrophiles is depicted



Scheme 6. Nitrimine-based cross-coupling reaction employed in the synthesis of phenprocoumon.

in Scheme 7. After the attack of the nucleophile in a Friedel–Crafts addition to the nitrimine (**2d**) and rearomatization, compound **8** is formed. Neighbouring-group-assisted extrusion of nitrous oxide and hydroxide yields the iminium ion **9**. The deprotonation of **9** by hydroxide generates the desired product **3b** and water. A Hammett analysis[15] of the reaction revealed a positive slope of $\rho = 1.35$, suggesting that the



Scheme 7. Proposed reaction pathway for formal $C(sp^2)$–$C(sp^2)$ cross-coupling reactions between selected heterocycles and nitrimine electrophiles.

mechanism involves the development of a negative charge or the disappearance of a positive charge in the transition state of the rate-determining step, plausibly the addition of the nucleophile to the nitrimine[16] or the deprotonation of the vinylic methane (**9**).[17] Experimentally, the detected evolution of gas and hydrolysis of the nitrimine without the use of molecular sieves led us to reason that N_2O gas and H_2O are produced in the reaction. Further investigations regarding the reaction mechanism are ongoing in our laboratory.

In summary, nitrimines effectively enable the assembly of new carbon–carbon bonds in a metal-free formal cross-coupling process. This synthetically valuable procedure tolerates a broad range of substrates allowing for the preparation of di- and trisubstituted alkenes with ease. Moreover, stereocontrol over the final alkene geometry is allowed by slight modification of the initial reaction conditions. The method is a useful approach for the metal-free syntheses of bioactive frameworks, especially popular drug targets. Ongoing studies in our laboratory are dedicated toward the further exploitation of nitrimines as reagents in metal-free chemical reactions.

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