Heterocycles

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# Nickel-Catalyzed Cycloaddition of 1,3-Dienes with 3-Azetidinones and 3-Oxetanones**

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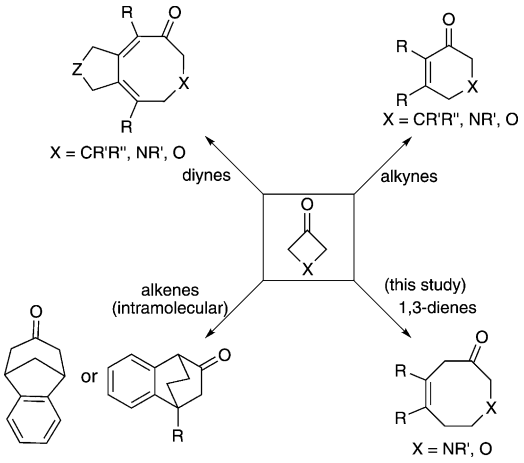
Both thermodynamic and kinetic forces make C–C bond activation one of the most difficult processes to facilitate.[1] Breaking the strong bond between two carbon atoms is further hampered by the increased steric congestion in C–C bonds relative to C–H and C–X bonds.[1a,b,2] Despite the difficulty associated with C–C bond activation, a handful of transition-metal-catalyzed methods have been developed.[1] In fact, these methods serve as potentially useful technology for the construction of complex molecular architectures from relatively simple starting materials in a highly atom-economical fashion. The C–C bond-activation step in these systems generally occurs by two important processes: 1) oxidative addition of the C–C bond to the transition metal, or 2) β-carbon elimination of transition-metal–alkyl complexes.[1a,j] Furthermore, the use of small cyclic systems wherein the release of inherent strain provides the necessary driving force for C–C bond cleavage has been a central theme of C–C bond activation strategies.[1,3,4]

Ito and co-workers pioneered the use of cyclobutanones as substrates in transition-metal-catalyzed reactions involving C–C bond activation.[5] Since then, a handful of processes involving the insertion of unsaturated hydrocarbons into the C–C bond of cyclobutanones have been developed. For example, Murakami and co-workers developed a nickel-catalyzed cycloaddition of alkynes and diynes with cyclobutanones to form six- and eight-membered carbocycles.[6a–d] Wender et al. reported the rhodium-catalyzed intramolecular [6+2] cycloaddition of activated cyclobutanones (i.e. 2-vinylcyclobutanones) and olefins to construct eight-membered carbocycles.[6e,f] Murakami and co-workers also demonstrated the use of Rh and Ni catalysts for intramolecular olefin insertion into cyclobutanones to form a variety of carbocycles.[6g–k] Furthermore, we and others independently disclosed syntheses of substituted 3-piperidones by the nickel-catalyzed cycloaddition of alkynes and 3-azacyclobutanones (3-azetidinones).[7] We successfully extended this concept to the synthesis of eight-membered heterocycles by the nickel-catalyzed insertion of diynes into 3-azetidinones (Scheme 1).[8]




***Scheme 1.*** Transition-metal-catalyzed C–C bond cleavage in cyclobutanones, 3-azetidinones, and 3-oxetanones.

Despite these recent advances in the C–C activation of cyclobutanones, the intermolecular insertion of 1,3-dienes remains a challenge. Interestingly, Ogoshi et al. have shown that 1,3-dienes do indeed react with cyclobutanones in the presence of typical Ni catalysts.[9] The $Ni^0$ complex undergoes oxidative coupling between the diene and the carbonyl group of the cyclobutanone, as is seen in numerous reductive coupling methodologies of unsaturated hydrocarbons and carbonyl compounds (i.e., aldehydes, ketones, carbon dioxide, isocyanates, etc.) with a reducing agent.[10,11] However, in the case of diene substrates, the β-carbon elimination necessary to complete a catalytic cycle does not occur, and thus a relatively stable catalyst sink results: an $\eta^3$:$\eta^1$-allylalkoxynickel(II) complex.[9] Thus, given the difficulties associated with catalyst turnover, we were delighted to discover effective conditions for the nickel-catalyzed cycloaddition of azetidinones and 1,3-dienes to afford eight-membered N heterocycles. Herein, we report these results.

The nickel-catalyzed cycloaddition was investigated with the commercially available diene **1a** and azetidinone **2a** as model substrates. Initially, highly σ-donating N-heterocyclic carbenes (NHCs) were explored as potential ligands for this reaction. However, although good conversion of the azetidinone was observed, none of the desired product was detected (Table 1, entries 1–3). Surprisingly, similar Ni/NHC systems

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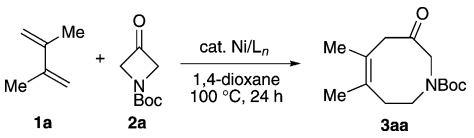
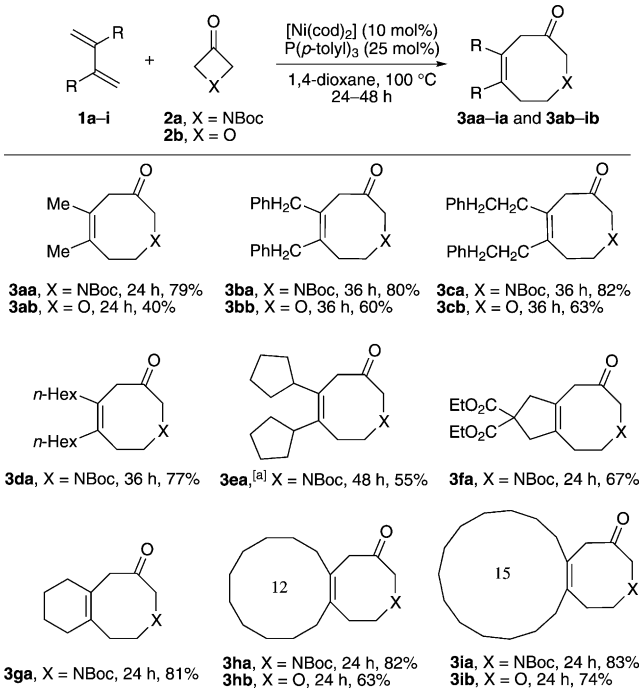
***Table 1:*** Ligand screening for the nickel-catalyzed cycloaddition of diene **1a** and azetidinone **2a**.[a]




**1a** **2a** **3aa**

| Entry | Ligand | Conversion [%][b] | Yield [%][c] |
|---|---|---|---|
| 1 | IPr | 83 | – |
| 2 | SIPr | 42 | – |
| 3 | IMes | 89 | – |
| 4 | dppf | 34 | n.d. |
| 5 | dppp | – | – |
| 6 | dppb | > **99** | **79** |
| 7 | $PCy_3$ | 25 | n.d. |
| 8 | $PPh_3$ | > 99 | 75 |
| 9 | $P(p\text{-}CF_3C_6H_4)_3$ | 59 | n.d. |
| 10 | $P(p\text{-}OMeC_6H_4)_3$ | 70 | n.d. |
| 11 | $P(p\text{-tolyl})_3$ | > **99** | **79** |

[a] Reaction conditions: diene **1a** (2 equiv), azetidinone (1 equiv, 0.4 M), $[Ni(cod)_2]$ (10 mol%), ligand (20 mol% for entries 1–3; 12 mol% for entries 4–6; 25 mol% for entries 7–11). [b] The conversion of **1a** was determined by GC with naphthalene as an internal standard. [c] Yield of isolated **3aa**. Boc = *tert*-butoxycarbonyl, cod = 1,5-cyclooctadiene, Cy = cyclohexyl, dppb = 1,4-bis(diphenylphosphanyl)butane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dppp = 1,3-bis(diphenylphosphanyl)propane, IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene; n.d. = not determined.

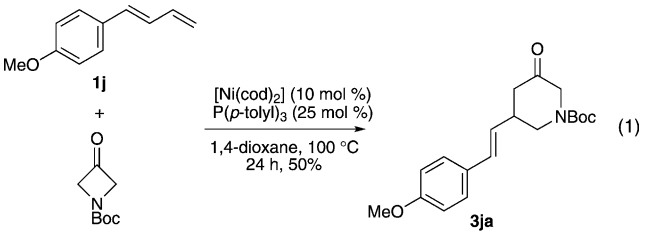


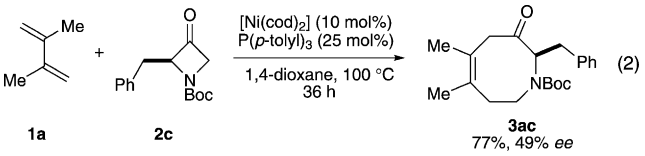

***Scheme 2.*** Nickel-catalyzed cycloaddition of 1,3-dienes with azetidinone **2a** and oxetanone **2b**. Reaction conditions: diene **1** (2 equiv), **2a** (1 equiv, 0.4 M) or **2b** (1 equiv, 0.2 M), $[Ni(cod)_2]$ (10 mol%), $P(p\text{-tolyl})_3$ (25 mol%), 1,4-dioxane, 100 °C. [a] A catalyst loading of 15 mol% was required.

have been reported to effectively catalyze the cycloaddition of diynes and enynes with carbonyl compounds.[8,12] Thus, azetidinone decomposition in this case could be attributed to the highly basic nature of these ligands in conjunction with the high temperature of the reaction. We then turned our focus toward less basic monodentate and bidentate phosphine ligands. Whereas dppf and dppp gave poor conversion of azetidinone (Table 1, entries 4 and 5), the use of dppb led to quantitative conversion and the isolation of product **3aa** in 79% yield (entry 6). Low conversion was observed with the monodentate ligand $PCy_3$ (Table 1, entry 7); however, the use of $PPh_3$, which has been recently reported to catalyze the coupling of alkynes and azetidinones, resulted in isolation of the cycloadduct in 75% yield (Table 1, entry 8). Following the discovery of $PPh_3$ as a simple and effective ligand, we evaluated other triaryl phosphine ligands for this reaction (Table 1, entries 8–11). The use of $P(p\text{-tolyl})_3$ consistently afforded the desired product in high yield.[13] Further optimization led to these final reaction conditions: $[Ni(cod)_2]$ (10 mol%), $P(p\text{-tolyl})_3$ (25 mol%), 1,4-dioxane, 100 °C, 24–48 h.

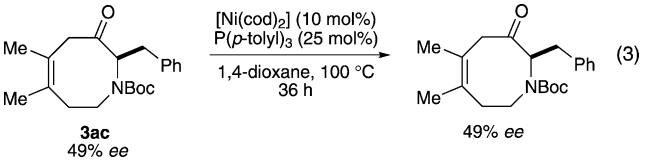
We explored the scope of this synthetic method under the optimized reaction conditions (Scheme 2). The reaction of oxetanone **2b** with the volatile diene **1a** afforded oxocine **3ab** in moderate yield. Dienes **1b** and **1c** bearing benzyl and homobenzyl substituents also underwent cycloaddition with both azetidinone **2a** and oxetanone **2b** to form the eight-membered N- and O-containing heterocycles **3ba**, **3bb**, **3ca**, and **3cb**. Dienes **1d** and **1e** bearing primary and secondary alkyl substituents, respectively, were well-tolerated in this cycloaddition and reacted with azetidinone **2a** to afford the azocine products **3da** and **3ea** in good yield. We recently reported the nickel-catalyzed cycloaddition of 1,6-diynes and 3-azetidinones to form azocine products with a fused 5,8 ring system.[8] The cycloaddition of the cyclic diene **1f** with 3-azetidinone **2a** afforded the similar 5,8-ring-fused cycloadduct **3fa** in good yield and thus complements our diyne–azetidinone cycloaddition. Our prior attempts to synthesize heterocycles with fused 6,8 ring systems by the cycloaddition of 1,7-diynes with a 3-azetidinone afforded the spirocyclic pyran products.[8] Gratifyingly, the 6,8-ring-fused azocine **3ga** was obtained in high yield by the use of diene **1g**. Owing to the interest in macrocyclic heterocycles,[14] we synthesized macrocyclic dienes **1h** and **1i** and subjected them to cycloaddition reaction conditions with both azetidinone **2a** and oxetanone **2b**. To our delight, the fused macrocyclic azocines and oxocines **3ha**, **3hb**, **3ia**, and **3ib** were obtained in high yields. The structure of **3hb** was determined unambiguously by single-crystal X-ray crystallography.[15] Interestingly, the reaction between unsymmetrical diene **1j** and 3-azetidinone **2a** afforded the substituted piperidinone **3ja**, rather than the expected product with an eight-membered azocine ring, in moderate yield [Eq. (1)].

To address the question of regioselectivity in the ring opening of 2-substituted azetidinones, we synthesized 2-benzyl-3-azetidinone (**2c**) and treated it under the cycloaddition conditions with diene **1a** [Eq. (2)]. Gratifyingly, only the regioisomer **3ac**[16] was obtained, in high yield, which suggests that preferential cleavage of the C–C σ bond between the carbonyl carbon atom and the unsubstituted

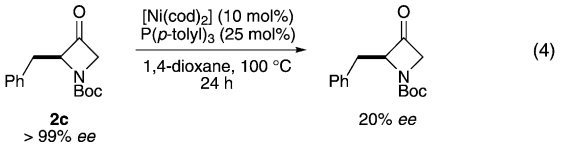


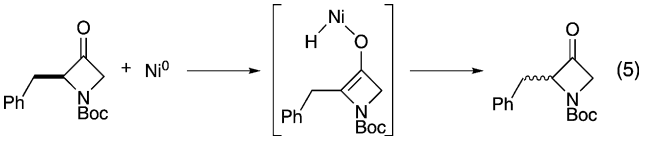

α carbon atom of the 3-azetidinone takes place to afford the heterocyclic product. Although the reaction was highly regioselective, the product was obtained with only 49% *ee*, in contrast with our previously reported cycloaddition of alkynes and 3-azetidinones, in which excellent retention of enantiomeric purity was observed when enantiomerically pure 2-substituted azetidinones were used.[7a] To rule out the possibility of nickel-catalyzed racemization of the product, we subjected the chiral eight-membered azocine product (49% *ee*) to our catalytic conditions [Eq. (3)]. No erosion of




enantiomeric purity was observed over the course of the reaction. However, upon the treatment of the enantiomerically pure 2-benzyl-3-azetidinone **2c** with the Ni catalyst in the absence of the diene but otherwise under the standard reaction conditions, significant loss of enantiomeric purity was observed in 24 h [Eq. (4)]. This observation suggests that

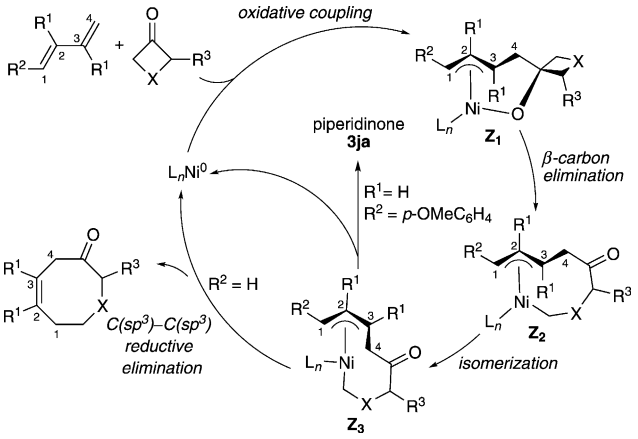



the chiral 3-azetidinone can undergo $C^{\alpha}$–H activation by Ni with the loss of enantioselectivity [Eq. (5)]. Ho and Aïssa also proposed the nickel-catalyzed $C^{\alpha}$–H activation of 3-azetidinones to explain the formation of the hydroalkynylation




product observed in the nickel-catalyzed cycloaddition of a 3-azetidinone and diphenylacetylene.[7b]

The proposed mechanism for this cycloaddition reaction is shown in Scheme 3. The oxidative coupling of the 1,3-diene and the carbonyl group of the 3-azetidinone/3-oxetanone




***Scheme 3.*** Proposed mechanism for the nickel-catalyzed cycloaddition reaction.

would result in the formation of an $\eta^3$:$\eta^1$-allylalkoxynickel(II) complex $\mathbf{Z_1}$.[9] This complex would then undergo β-carbon elimination to afford the intermediate $\mathbf{Z_2}$. In the case of 2-substituted azetidinones, β-carbon elimination would occur from the less hindered side of the azetidinone, that is, with cleavage of the C–C bond between the carbonyl carbon atom and the unsubstituted α carbon atom of the 3-azetidinone. Complex $\mathbf{Z_2}$ would then isomerize to complex $\mathbf{Z_3}$, which can undergo two different $C(sp^3)$–$C(sp^3)$ reductive-elimination pathways to form either the piperidinone or the eight-membered heterocyclic product. C–C bond-forming reductive elimination of the $\eta^3$:$\eta^1$-allylalkylnickel(II) complex $\mathbf{Z_3}$ generally yields the eight-membered heterocyclic product, as observed with dienes **1a–i**. However, to explain the formation of the six-membered heterocycle **3ja** when diene **1j** was used, in this case reductive elimination must occur at the C3 position of the $\eta^3$:$\eta^1$-benzylalkylnickel(II) complex $\mathbf{Z_3}$ owing to stabilization by the phenyl group.[17]

In conclusion, we have developed a Ni/P(*p*-tol)$_3$-catalyzed intermolecular cycloaddition of 1,3-dienes and 3-azetidinones/3-oxetanones. This synthetic method involves C–C activation of the strained four-membered heterocycle to form monocyclic and bicyclic eight-membered heterocyclic products, which are difficult to access by conventional methods. Interestingly, the use of a diene conjugated with a benzene ring led to the formation of a piperidinone rather than an eight-membered heterocycle. Efforts to expand the scope of the reaction and mechanistic analysis are in progress.

## Experimental Section

General procedure: In a nitrogen-filled glove box, a solution of the catalyst (10 mol%; prepared from $[Ni(cod)_2]$ and tri(*p*-tolyl)phosphane in a 1:2.5 molar ratio in 1,4-dioxane) was added to a solution of

the 3-azetidinone (1 equiv, 0.4 M) and the 1,3-diene (2 equiv) in 1,4-dioxane at room temperature. The resulting reaction mixture was stirred for 24 h at 100 °C and then opened to air, concentrated in vacuo, and purified by silica-gel flash column chromatography.

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