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Nickel-Catalyzed Cycloaddition of Vinylcyclopropanes to Imines

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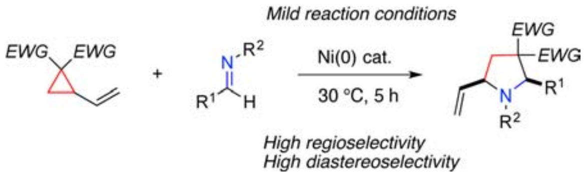
ABSTRACT



Nickel-catalyzed intermolecular [3 + 2] cycloaddition of vinylcyclopropanes to imines has been developed. This transformation generates substituted pyrrolidines in high yields, with good regio- and diastereo- selectivity under mild reaction conditions. A variety of imines can be used in this reaction. An asymmetric variant of the reaction has also been demonstrated.

Pyrrolidines are important structural units in organic chemistry and are frequently found in primary and secondary metabolites as well as in other biomolecules and synthetic pharmaceuticals.[1] Therefore, significant effort has been devoted to the efficient stereoselective synthesis of functionalized/substituted pyrrolidines.[2]

Transition-metal-catalyzed intermolecular cycloaddition is a powerful method for the construction of highly substituted heterocycles since it allows for high levels of complexity and multiple bond formation in a single step, with good atom economy (Scheme 1).[3] Tsuji for the first time carried out palladium-catalyzed [3 + 2] cycloadditions of vinylcyclopropanes (VCPs, **1a**) to aryl isocyanates as potent electrophiles for the synthesis of γ-lactams.[4,5] Recently, Johnson reported the palladium-catalyzed [3 + 2] cycloaddition of VCPs to aldehydes for the formation of tetrahydrofurans.[6] The key intermediate in these reactions was an acyclic zwitterionic π-allylpalladium species **A**, which was formed from ring-opening of the VCP by oxidative addition to Pd(0). We anticipated that Ni(II) would be a sufficiently stronger Lewis acid than Pd(II) to be effective in cycloaddition.[7,8] A heteronickelacycle is well-known to play an important role as a key intermediate in catalytic reactions.[9] We hypothesized that coordination of an imine to an oxanickelacycle would be followed by nucleophilic attack of the VCP toward the imine, eventually resulting in diastereoselective cycloaddition,

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[1] (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603.

[2] Recent examples: (a) Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 7297. (b) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (c) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (d) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646. (d) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (e) Kumar, I.; Mir, N. A.; Gupta, V. K.; Rajnikant *Chem. Commun.* **2012**, *48*, 6975.

[3] Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

[4] Examples of cycloaddtion of trimethylenemethanes (TMMs) with imines: Trost, B. M; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636. Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398. Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2010**, *132*, 8238.

[5] Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157.

[6] Parsons, A. T.; Champbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541.

[7] For Lewis acid catalyzed ring opening of VCP and subsequent addition to imines, see: (a) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (b) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B. *J. Am. Chem. Soc.* **2012**, *134*, 5048. (c) Kang, Y.-B.; Tang, Y.; Sun, X.-L. *Org. Biomol. Chem.* **2006**, *4*, 299. (d) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688.

[8] (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Bugarin, A.; Connell, B. T. *Organometallics* **2008**, *27*, 4357. (c) Li, K.; Xue, D. *J. Phys. Chem. A* **2006**, *110*, 11332. (d) Schubert, W. M.; Murphy, R. B.; Robins, J. *Tetrahedron* **1962**, *17*, 199. (e) Huheey, J. E. *J. Org. Chem.* **1971**, *36*, 204.

[9] For some examples of crystallographic analysis of heteronickelacycles, see: (a) Karsch, H. H.; Leithe, A. W.; Reisky, M.; Witt, E. *Organometallics* **1999**, *18*, 90. (b) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (c) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802.

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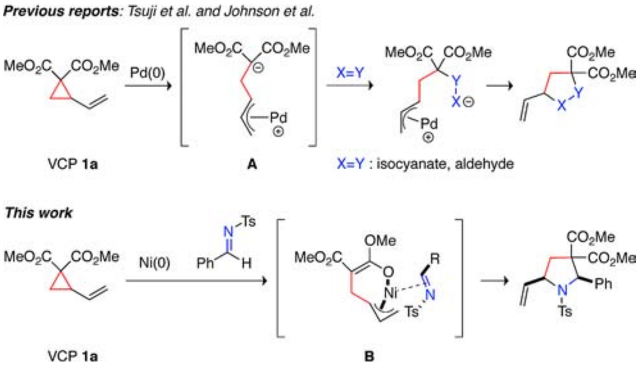
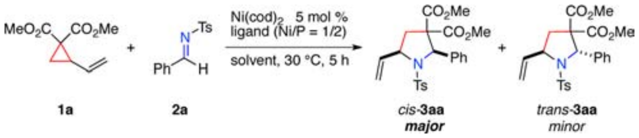
Scheme 1. Transition-Metal-Catalyzed [3 + 2] Cycloaddition



because this type of reaction proceeds via a cyclic intermediate **B**.[10,11] In this study, we successfully proved this hypothesis. Herein, we demonstrated the Ni(0)-catalyzed cycloaddition of vinylcyclopropanes and imines to afford pyrrolidines with high regio- and diastereoselectivity.

Table 1. Nickel-Catalyzed Cycloaddition of **1a** with **2a**[a]

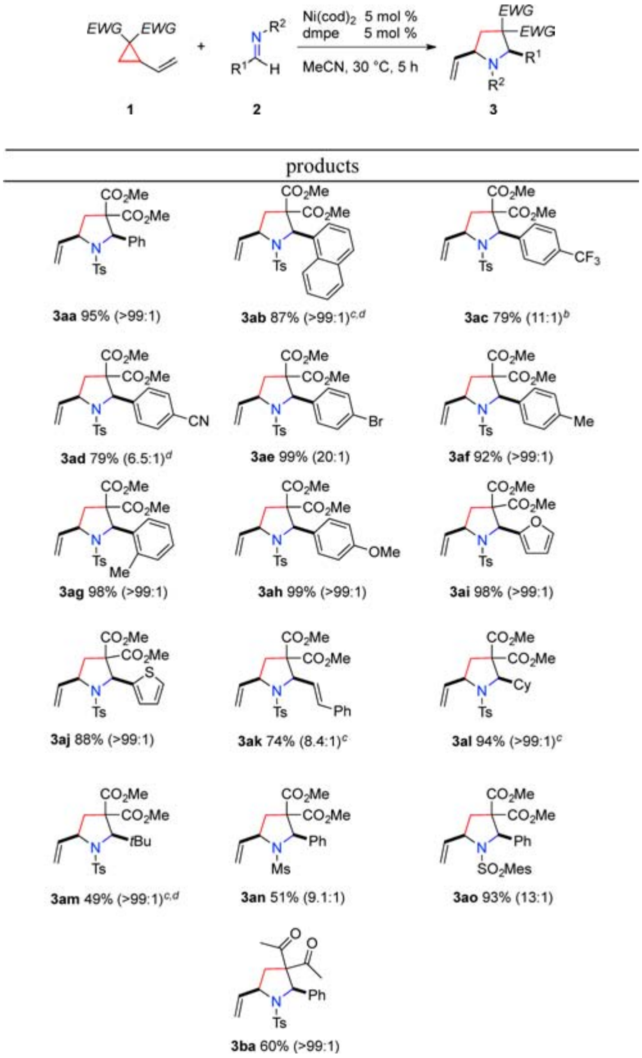


entry	ligand	solvent	yield[b] (%)	dr[c]
1	PMe_3	CH_3CN	62	6.0:1
2	PMe_2Ph	CH_3CN	47	3.3:1
3	$PMePh_2$	CH_3CN	55	3.1:1
4	PPh_3	CH_3CN	60	6.5:1
5	PCy_3	CH_3CN	34	2.5:1
6	dppe	CH_3CN	73	5.2:1
7	dmpe	CH_3CN	>99 (95)	>99:1
8	dmpe	^{i}PrOH	82	>99:1
9	dmpe	THF	65	>99:1
10	dmpe	toluene	25	>99:1

[a] Reactions were carried out using Ni(cod)$_2$ (5 mol %), ligand, **1a** (5 mol %), and **2a** (0.30 mmol) in 1 mL of solvent for 5 h in a sealed tube. [b] Determined by ^{1}H NMR analysis using $CHBr_3$ as internal standard. Isolated yield shown in parentheses. [c] Diastereomeric ratio between *cis*-**3aa** and *trans*-**3aa** was determined by ^{1}H NMR analysis. dppe: 1,2-Bis(diphenylphosphino)ethane. dmpe: 1,2-Bis(dimethylphosohino)-ethane.

Our study began with the reaction of vinylcyclopropane **1a** with *N*-tosylbenzaldimine **2a** in the presence of the Ni(cod)$_2$/PMe_3 catalyst system. The reaction of **1a** with **2a** in CH_3CN in the presence of 5 mol % of Ni(cod)$_2$ and 10 mol % of PMe_3 at 30 °C for 5 h afforded the corresponding pyrrolidine **3aa** in 62% yield, although the *cis*/*trans* diastereoselectivity was 6.0:1 (Table 1, entry 1). The major diastereomer *cis*-**3aa** was confirmed by X-ray crystal structure analysis. Optimization of the nickel catalyst, i.e., the use of Ni(cod)$_2$ and 1,2-bis(dimethylphosphino)-ethane (dmpe), selectively afforded *cis*-**3aa** in excellent yield with high diastereoselectivity, and *trans*-**3aa** was not formed (entry 7). The use of other monodentate or bidentate phosphine ligands gave inferior results (entries 2−6). From among the various solvents examined, CH_3CN gave the best results, affording **3aa** in quantitative yield (entries 8−10). When $NiCl_2$ catalyst was used, no reaction occurred, which suggested that a mechanism involving a Ni(II) Lewis acid is unlikely. No reaction occurred when a catalyst system without Ni(cod)$_2$ or dmpe was used.

Table 2. Scope of Nickel-Catalyzed Cycloaddition[a]



3aa 95% (>99:1)
3ab 87% (>99:1)[c,d]
3ac 79% (11:1)[b]
3ad 79% (6.5:1)[d]
3ae 99% (20:1)
3af 92% (>99:1)
3ag 98% (>99:1)
3ah 99% (>99:1)
3ai 98% (>99:1)
3aj 88% (>99:1)
3ak 74% (8.4:1)[c]
3al 94% (>99:1)[c]
3am 49% (>99:1)[c,d]
3an 51% (9.1:1)
3ao 93% (13:1)
3ba 60% (>99:1)

[a] Reactions were carried out using Ni(cod)$_2$ (5 mol %), dmpe (5 mol %), **1** (0.25 mmol), and **2** (0.30 mmol) in 1 mL of CH_3CN at 30 °C for 5 h in a sealed tube. Isolated yield is shown. Diastereomeric ratio is shown in parentheses. [b] Reaction performed for 10 h. [c] Reaction performed for 24 h. [d] Reaction performed at 50 °C. EWG: electron-withdrawing group. Cy: cyclohexyl. Mes: mesityl.

We next investigated the scope of vinylcyclopropanes **1** and imines **2** that can be used in the reaction (Table 2). Under the optimized conditions, the reaction of **1a** with **2a**

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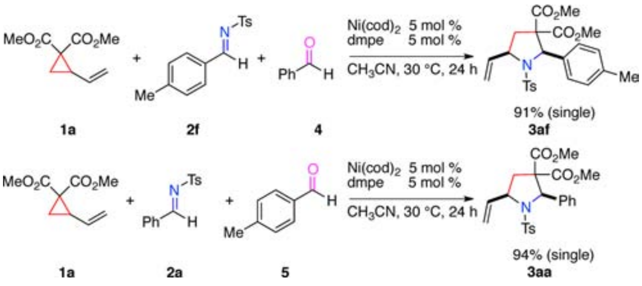
(10) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930.

(11) Mori, T.; Nakamura, T.; Kimura, M. *Org. Lett.* **2011**, *13*, 2266.

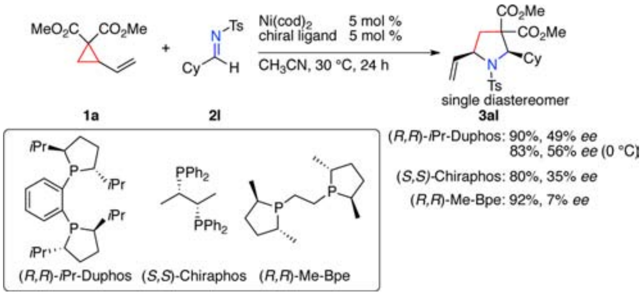
gave **3aa** in 95% isolated yield. *N*-Tosyl-1-naphthaldimine also gave **3ab** in good yield when the reaction was prolonged to 24 h and the temperature was increased to 50 °C. Electron-deficient aromatic aldimines also underwent this reaction to afford pyrrolidine derivatives such as **3ac** and **3ad** in good yield, but the diastereoselectivity was slightly low, 11:1 and 6.5:1, respectively. Surprisingly, an aromatic aldimine possessing a bromo group selectively gave the desired cycloadduct **3ae**, instead of the oxidative insertion of Ni(0) into the C−Br bond. On the other hand, this method worked best for electron-rich aromatic aldimines and heteroaromatic aldimines in terms of both yield and diastereoselectivity (**3af**, **3ag**, **3ah**, **3ai**, and **3aj**). When cinnamylaldimine was used, the reaction afforded cycloadduct **3ak**. Aliphatic imines such as cyclohexyltosylimine and *tert*-butyltosylimine also underwent this reaction to give **3al** and **3am**, respectively. *N*-mesylimine and *N*-mesitylsulfonylimine underwent [3 + 2] cycloaddition with **1a** to give **3an** and **3al**, respectively; however, no reaction occurred when using *N*-Ph imine or *N*-Ns imine (Ns: 2-nitrobenzenesulfonyl). The reaction of 1,1-diacyl-2-vinylcyclopropane **1b** with **2a** gave **3ba** diastereoselectively in 60% yield[12] Furthermore, a chemoselective reaction was demonstrated by the [3 + 2] cycloaddition of **1a** with an imine in the presence of an aldehyde (Scheme 2). The reaction proceeded effectively to afford the desired pyrrolidine product **3af** or **3aa** in high yields (>91%). No cycloadduct of **1a** and the aldehyde was observed in any case.

Scheme 2. Chemoselective Cycloaddition



An asymmetric version of this highly regio- and diastereoselective reaction was attempted. A preliminary study showed that the reaction of **1a** with **2l** affords **3al** in 90% yield and with 49% ee when (*R,R*)-*i*-Pr-Duphos was employed as a chiral phosphine ligand (Scheme 3). Other chiral ligands such as (*S,S*)-Chiraphos and (*R,R*)-Me-Bpe also gave **3al** in good yields (80% and 92%) but with lower enantioselectivity (35% ee and 7% ee). However, the enantioselectivity was improved up to 56% ee, with 83% yield, when the reaction was carried out at 0 °C using (*R,R*)-*i*-Pr-Duphos as a chiral ligand.

Scheme 3. Asymmetric Cycloaddition



In summary, we have demonstrated the nickel-catalyzed [3 + 2] cycloaddition of vinylcyclopropanes to imines to obtain pyrrolidine derivatives with high diastereoselectivities. A nickel catalytic system and the coordination of a tosyl substituent to nickel effectively promoted diastereoselective cycloaddition, and various polysubstituted pyrrolidines could be synthesized under mild reaction conditions. Detailed studies to elucidate the underlying reaction mechanism and efforts to improve the enantioselectivity of asymmetric [3 + 2] cycloaddition are underway.

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Supporting Information Available. Experimental procedures including spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Bowman, R. K.; Johnson, J. S. *Org. Lett.* **2006**, *8*, 573.

The authors declare no competing financial interest.