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Ni-Catalyzed Alkenylation of Triazolopyridines: Synthesis of 2,6-Disubstituted Pyridines

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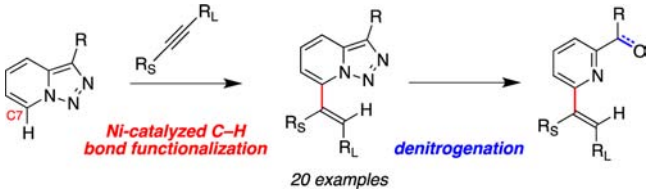
ABSTRACT



A synthetic strategy to access 2,6-disubstituted pyridines from triazolopyridines through a regioselective nickel-catalyzed alkenylation reaction of the C7−H bond is described. The N_2 fragment embedded in the resulting C−H functionalized triazolopyridine can be readily excised using acidic or oxidative conditions to unmask the pyridine.

Achieving selective transition-metal-catalyzed C−H bond functionalization of *N*-heterocycles[1] continues to inspire research groups worldwide because these structural motifs are ubiquitous in compounds with significant biological activity or in materials with promising electronic properties.[2,3] Pyridines have proved to be recalcitrant substrates in C−H bond functionalization processes because of their electron-poor π-system and Lewis basic N-atom, which together thwart the use of electrophilic C−H bond activation transition metal complexes.[4] While metal-catalyzed C−H functionalization methods have emerged that overcome these challenges,[5] these methods are generally restricted to pyridines lacking a 2-substituent; the presence of this group often significantly reduces the yield of the 2,6-disubstituted product.[6] To diminish the detrimental effect of the Lewis basic pyridine nitrogen, pyridine *N*-oxides[7] or *N*-imines[8] were used as protected pyridines. While these methods exhibit a greater tolerance to transition metals, the scope of the reaction is attenuated by the solubility of the substrate, and removal of the *N*-protecting group requires a separate step, which does not not result in new bond

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(7) Cf. (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (c) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (d) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (e) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

(8) (a) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2010**, *49*, 1115.

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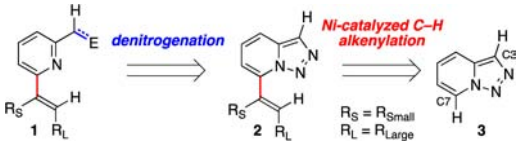
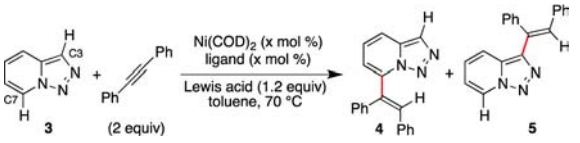
formation. We anticipated that these drawbacks might be surmounted using triazolopyridines as pyridine surrogates:[9] a new C−O bond is produced upon excision of the embedded N_2 molecule to produce a 2,6-disubstituted pyridine (Scheme 1).[10] Despite the potential for triazolopyridines to function as masked pyridines, no C−H bond activation methodology exists that employs them as substrates. Herein, we report the development of a general, regiospecific Ni-catalyzed heteroarylation of internal acetylenes with triazolopyridines.

Scheme 1. Synthesis of 2,6-Disubstituted Pyridines from C−H Bond Functionalization−Denitrogenation of Triazolopyridines



In search of a general set of conditions, a range of transition metal complexes and ligands were screened for the alkenylation of triazolopyridine **3** with diphenylacetylene. Triazolopyridine **3** was selected because either the C3−H or C7−H bond could potentially be functionalized, and diphenylacetylene was chosen as the alkyne because it performs poorly in existing methods for the alkenylation of pyridine.[5c] We anticipated if optimal conditions were found to achieve the regiospecific functionalization of **3** with diphenylacetylene that a general alkenylation method would result. Established transition metal C−H bond activation catalysts were first examined,[11] and $Ni(COD)_2$ emerged as a potential catalyst from this initial screen. No productive reaction was observed with Rh(I) or Ir(I) complexes, all potent heteroarylation catalysts. While no reaction was observed using $Ni(COD)_2$ and bidentate phosphine ligands, the desired alkenylation could be triggered using monodentate phosphines with the highest yield obtained using the inexpensive, air stable triphenylphosphine (Table 1, entries 2−6). The catalyst loading could be reduced to 3 mol % without attenuation of the yield of the reaction (entries 6−8). The identity of the Lewis acid was crucial to the success of this reaction with the best conversions using $AlMe_3$; reduced conversion was observed using substoichiometric amounts of $AlMe_3$, and using weaker Lewis acids such as triphenylborane or dimethylzinc resulted in no reaction (entries 11−13). The success of our reaction depended on the order of addition of the Lewis acid: high yields were obtained reproducibly only when the triazolopyridine was premixed with $AlMe_3$ before addition of a solution of phosphine and $Ni(COD)_2$. The optimal solvent was found to be toluene; diminished yields were observed using ethereal or chlorinated solvents.[11] While alkenylation could potentially occur at either the C3 or C7 position, reaction occurred exclusively at C7 to afford only **4** as a single isomer. This reactivity is orthogonal to KOH-mediated iodination, which occurs exclusively at C3.[12] In contrast to previous studies on the alkenylation of pyridine,[5c] we observed only the insertion of a single diphenylacetylene molecule.

Table 1. Optimization of C7-Alkenylation of Triazolopyridine



entry	$Ni(COD)_2$ (mol %)	ligand	mol %	Lewis acid	% yield **4**[a,b]
1	10	–	–	$AlMe_3$	n.r.
2	10	dppb	5	$AlMe_3$	n.r.
3	10	PCy_3	10	$AlMe_3$	56
4	10	$PPhCy_2$	10	$AlMe_3$	73
5	10	PPh_2Cy	10	$AlMe_3$	85
6	5	PPh_3	10	$AlMe_3$	>95
7	5	PPh_3	5	$AlMe_3$	>95
8	3	PPh_3	3	$AlMe_3$	>95
9	2	PPh_3	2	$AlMe_3$	71
10[c]	3	PPh_3	3	$AlMe_3$	64
11	3	PPh_3	3	$AlCl_3$	14
12	3	PPh_3	3	BPh_3	<5
13	3	PPh_3	3	$ZnMe_2$	<5

[a] As determined using ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] E/Z = >95:5. [c] 0.2 equiv of $AlMe_3$ used.

A series of triazolopyridines **3** were examined to determine the scope and limitations of our Ni-catalyzed alkenylation reaction (Table 2).[13] Our reaction proved robust tolerating alkyl substitution at any position on triazolopyridine without diminishment of the reaction yield (entries 1−6). Electron-donating or -withdrawing groups could be appended to the triazolopyridine without adversely affecting the yield of the alkenylation (entries 7−10). While our alkenylation reaction tolerated the presence of a tertiary amine, the olefin E/Z selectivity was attenuated (entry 8). In contrast, the olefin selectivity was not diminished when the steric or electronic environment around the C7−H bond was modified with a C6-methyl or C6-F substituent (entries 9 and 10). In both cases, triazolopyridines **4i** and **4j** were obtained as single isomers.

The effect of changing the identities of the alkyne substituents on the C7-alkenylation reaction was investigated

(9) (a) Jones, G.; Sliskovic, D. R. *Tetrahedron Lett.* **1980**, *21*, 4529. (b) Jones, G.; Mouat, D. J.; Tonkinson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2719.

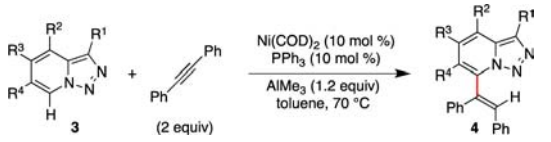
(10) For related strategies of traceless bond construction, see: (a) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89. (b) Guo, F.; Konkol, L. C.; Thomson, R. J. *J. Am. Chem. Soc.* **2010**, *133*, 18. (c) Mundal, D. A.; Avetta, C. T.; Thomson, R. J. *Nat. Chem.* **2010**, *2*, 294.

(11) Refer to the Supporting Information for a complete listing of the reaction conditions that were screened.

(12) Abarca, B.; Aucejo, R.; Ballesteros, R.; Blanco, F.; García-España, E. *Tetrahedron Lett.* **2006**, *47*, 8101.

(13) To simplify the manipulation of $Ni(COD)_2$ and Ph_3P when 0.2 mmol of the triazolopyridine was used, our investigations into the scope of our reaction were performed using 10 mol % of catalyst and phosphine.

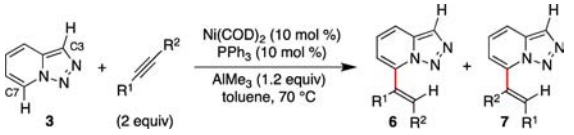
Table 2. Scope of the Ni-Catalyzed C7-Alkenylation Reaction

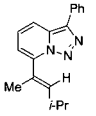
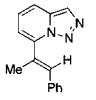
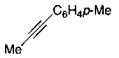
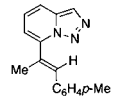
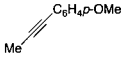
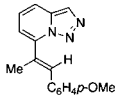
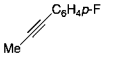
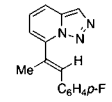
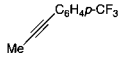
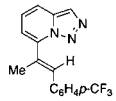
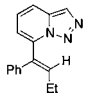


entry	#	R^1	R^2	R^3	R^4	**4** yield, %[a]
1	a	H	H	H	H	97
2	b	Me	H	H	H	93
3	c	Ph	H	H	H	94
4	d	H	Me	H	H	95
5	e	Me	H	Me	H	95
6	f	H	–CH=CH–CH=CH–		H	96
7	g	H	H	OMe	H	81
8	h	H	H		H	80[b]
9	i	H	H	H	Me	85
10	j	Me	H	H	F	71

[a] Isolated yield of **4** after silica gel chromatography, E/Z > 95:5. [b] 92:8 mixture of olefins.

Table 3. Regioselective C7-Alkenylation of Triazolopyridine



entry	alkyne	major triazolopyridine	#	yield, %[a] (**6**:**7**)
1			a	97 (R = *p*-Tol)
2			b	70 (R = Et)
3			c	76 (R = *n*-Pr)
4			d	82 (>95:5)
5			e	95 (85:15)
6			f	90 (86:14)
7			g	86 (81:19)
8			h	51 (70:30)
9			i	n.r.
10[b]			j	75 (20:80)

[a] Isolated yield of **6** and **7** after silica gel chromatography, E/Z > 95:5. [b] 10 mol % of PCy_3 used.

next (Table 3). While no insertion was observed with terminal- or silyl-substituted acetylenes,[14] the reaction tolerated a range of aryl- and alkyl-substituted alkynes. A slight attenuation of the reaction yield was observed with dialkyl acetylenes in comparison to diaryl acetylenes (entries 1–3). To our delight, alkyne insertion into the C7–H bond proved to be regioselective.[15] Triazolopyridine **6d** was formed as a single alkene isomer from the insertion of 4-methylpent-2-yne (entry 4). Regioselective alkyne insertion was also observed for aryl acetylenes with slightly higher selectivities observed for electron-rich arenes (entries 5–8). In each case the alkyne insertion occurred to form a new bond between C7 and the methyl-substituted acetylenic carbon. The sensitivity of our alkenylation reaction to the electronic nature of the alkyne is illustrated in the lower conversions observed with electron-deficient aryl acetylenes (entries 8 and 9). The regioselectivity of alkyne insertion was reversed when the methyl was replaced with an ethyl group to favor the formation of triazolopyridine **7j** (entry 10). If alkyne insertion is under steric control,[15] then this process finds phenyl to be smaller than the ethyl group.

The reactivity trends of our substrates in combination with the reported mechanism studies of nickel(0) complexes suggest that C7-alkenylation of triazolopyridines occurs through a Ni-catalyzed C–H bond activation pathway (Scheme 2). Before entering the catalytic cycle, the triazolopyridine **3** coordinates to $AlMe_3$ to produce **8**.[16] Coordination of the nickel catalyst with the aluminate positions it for selective oxidative addition of the C7–H bond in **9**.[16d,17] Oxidative addition then produces nickel(II) **10**, which undergoes regioselective alkyne insertion to form **11**, where the new C–C bond is formed between the smaller

(14) Precipitation of nickel black was observed when these acetylenes were used.

(15) The regioselectivity of alkyne insertion mirrors that of other Ni-catalyzed processes. For example, see: (a) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (c) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304. (d) Kumar, P.; Louie, J. *Org. Lett.* **2012**, *14*, 2026.

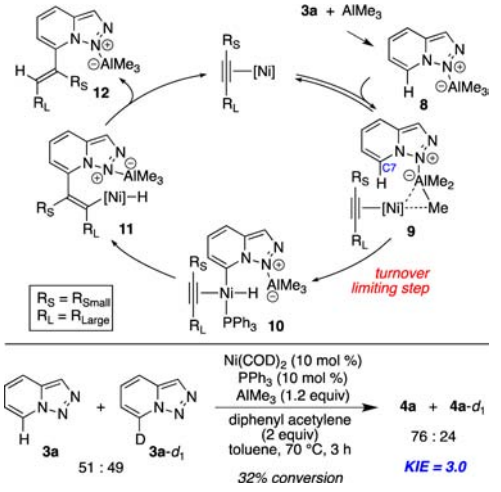
(16) (a) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (b) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627. (c) Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636. (d) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810. (e) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887.

(17) For related mechanistic studies on the oxidative addition of C–H bonds to Ni(0) complexes, see: (a) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845. (b) Reinhold, M.; McGrady, J. E.; Perutz, R. N. *J. Am. Chem. Soc.* **2004**, *126*, 5268. (c) Normand, A. T.; Hawkes, K. J.; Clement, N. D.; Cavell, K. J.; Yates, B. F. *Organometallics* **2007**, *26*, 5352. (d) Kanyiva, K. S.; Kashihara, N.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *Dalton Trans.* **2010**, *39*, 10483.

(18) For computational studies on the origin of the regioselectivity of Ni-promoted alkynyl processes, see: (a) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2050. (b) Liu, P.; Montgomery, J.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 6956.

alkynyl substituent and C7 of the triazolopyridine.[15,18] Reductive elimination then produces **12**.[19] Our data point to coordination of the substrate with the Lewis acid occurs first because successful C7-alkenylation requires preincubation of the triazolopyridine with $AlMe_3$ before addition of the nickel catalyst.

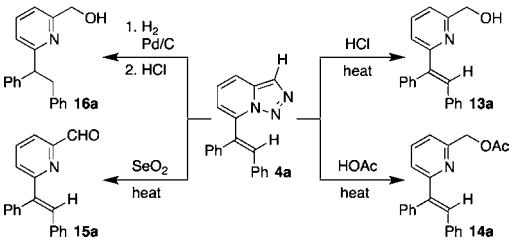
Scheme 2. Potential Catalytic Cycle



To gain insight into the catalytic cycle, we examined the reactivity of C7-labeled triazolopyridine **3a**-d_1 toward our reaction conditions. A kinetic isotope effect of 3.0 was observed for an intermolecular competition experiment between **3a**-d_0 and **3a**-d_1. This primary kinetic isotope effect indicates that C−H bond activation is the turnover-limiting step in the catalytic cycle.[20] No H/D exchange was observed in either the reisolated substrates or the product triazolopyridines. This absence indicates that proton exchange processes are not occurring between the nickel hydride and $AlMe_3$ or another substrate molecule.[21]

We next sought to demonstrate that our triazolopyridines functioned as masked pyridines through denitrogenation (Scheme 3). While our attempts to excise the N_2 fragment of the triazolopyridine using transition metal complexes were unsuccessful,[22] exposure of **4a** to acid or an oxidant produced the desired 2,6-disubstituted pyridine (Scheme 3).[9] A new C−O bond could be introduced without affecting the alkenyl substituent using either aqueous HCl to afford alcohol **13a** or HOAc to afford acetate **14a**, whereas oxidation with SeO_2 produced aldehyde **15a**. A one-flask hydrogenation−hydrolysis sequence was also achieved to produce alkyl-substituted pyridine **16a**.

Scheme 3. Conversion of Triazolopyridine **4a** into 2,6-Disubstituted Pyridines



In conclusion, we have developed a synthetic strategy to access 2,6-disubstituted pyridines from triazolopyridines through a regioselective Ni-catalyzed alkenylation of the C7−H bond. The N_2 fragment embedded in the resulting C−H functionalized triazolopyridine can be readily excised using acidic or oxidative conditions without destruction of the C7-alkene substituent. Our nickel alkenylation method employs the cheap and air stable triphenylphosphine ligand and a slight excess of the acetylene. It is tolerant of a range of functionality on either the triazolopyridine or alkyne without attenuation of the reaction yield. Importantly, alkyne insertion into the C7−H triazolopyridine bond is regioselective. Together, we believe that these attributes produce an attractive solution to the synthesis of polysubstituted pyridines.

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Supporting Information Available. Complete experimental procedures, spectroscopic and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(19) $AlMe_3$ could also accelerate reductive elimination; see: Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.

(20) In contrast, a KIE of 1 was observed for Ni(0)-catalyzed hydrofluoroarylation of alkynes. See ref 17d.

(21) H/D exchange processes are common in Pt-mediated C−H bond activation processes; see: Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 5961.

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