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Intermolecular Alkyne Hydroaminations Involving 1,1-Disubstituted Hydrazines

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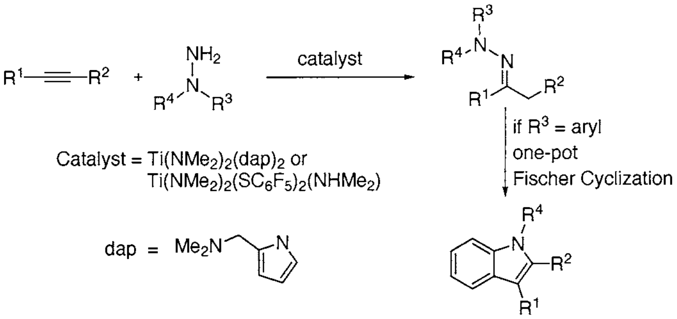
ABSTRACT



Two readily prepared catalysts have been developed for the hydroamination of alkynes by 1,1-disubstituted hydrazines. The catalyses are facile with terminal alkynes and some internal alkynes. If the hydrazine bears an aryl group, Fischer cyclization can occur in a one-pot procedure. In addition, reactions with acetylene to produce a plethora of hydrazones are described. Catalytic reactions involving acetylene and substituted hydrazines are complete in less than 2 h at room temperature and 1 atm of pressure.

Intermolecular hydroamination[1] of alkynes[2] by primary amines is a method for generating Schiff bases with perfect atom economy. Several catalysts, spanning much of the periodic table, have been utilized in the hydroamination of alkynes. Of particular interest have been catalysts incorporating rhodium,[3] palladium,[4] ruthenium,[5] lanthanides,[6] actinides,[7] and titanium.[8,9]

In this report, we describe catalysts for the direct addition of 1,1-dialkyl-substituted hydrazines to unactivated[10] alkynes, a new catalytic transformation.[11] Group IV hydroamination

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[1] Reviews relevant to hydroamination: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (b) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1. (c) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163.

[2] Leading examples of intermolecular hydroamination of alkenes: (a) Hartung, C. G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157−5162. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547. (c) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem.* **1999**, 1121−1132. (d) Trauthwein, H.; Tillack, A.; Beller, M. *Chem. Commun.* **1999**, 2029−2030. (e) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306−1319. (f) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E.; Zapf, A. *J. Organomet. Chem.* **1998**, *566*, 277−286. (g) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225−2226.

[3] Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339−6343.

[4] (a) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570−4571. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199−207.

[5] Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222−3225.

[6] (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (b) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772.

[7] (a) Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017−5035. (b) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773−3775. (c) Straub, T.; Frank, W.; Reiss, G. J.; Eisen, M. S. *J. Chem. Soc., Dalton Trans.* **1996**, 2541−2546.

[8] (a) Pohlki, F.; Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305−2308. (b) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924. (c) Siebeneicher, H.; Doye, S. *J. Prakt. Chem. Chem. Ztg.* **2000**, *341*, 102−106. (d) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389−3391. (e) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2001**, 4411−4418. (f) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967−3969. (g) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011−5013.

[9] Seminal mechanistic studies on Group IV metal-catalyzed hydroamination: (a) Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632−4635. (b) Sweeney, Z. K.; Salsman, J. L.; Anderson, R. A.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2339−2343. (c) Polse, J. L.; Anderson, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 13405−13414. (d) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753−2763. (e) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719.

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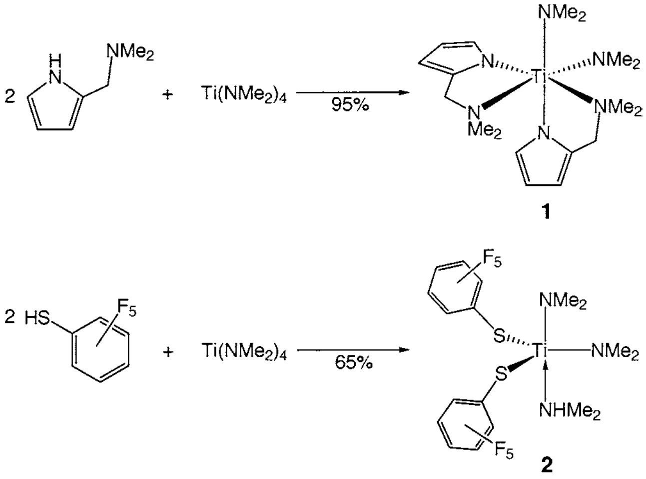
reactions involving primary amines and 1,1-disubstituted hydrazines should be differentiated by electronic effects in some key intermediates and chelation effects with both nitrogens of the hydrazine bonding in the same complex.[12] With these effects in mind, it is perhaps not surprising that some catalysts that efficiently catalyze hydroamination of alkynes with primary amines such as $Ti(NMe_2)_4$ and $Ti(NMe_2)_2(dpma)$[8f−g,13] are inefficient for hydrazines providing very low turnover numbers (less than 3) and slow reactions. Consequently, we investigated new catalyst designs for use with hydrazines. The result of the catalyst design studies is the new titanium complexes shown in Scheme 1.

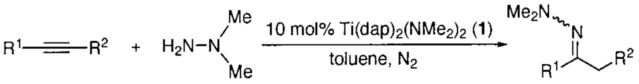
Scheme 1. Synthesis of Titanium Catalysts $Ti(NMe_2)_2(dap)_2$ (**1**) and $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$ (**2**)



The pyrrolyl titanium complex, $Ti(NMe_2)_2(dap)_2$ (**1**), was prepared from 2 equiv of α-(dimethylaminomethyl)pyrrole[14] (Hdap) and $Ti(NMe_2)_4$.[15] A second catalyst, five-coordinate $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$ (**2**), was produced from two equiv of commercially available pentafluorophenylthiol and $Ti(NMe_2)_4$.

Because of differing electronic[16] and chelation[17] factors, reactions involving hydrazines with electron-donating substituents are expected to be more difficult to catalyze.

Table 1. Alkyne Hydroamination by 1,1-Dimethylhydrazine with $Ti(NMe_2)_2(dap)_2$ (1) as Catalyst



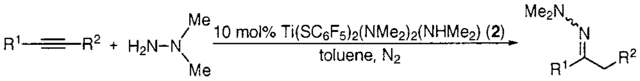
alkyne	temp (°C)	time (h)	% yield[a] (Markovnikov:anti-Markovnikov)	E:Z[c]
Bu^n−≡−H	75	24	79 (50:1)	3:2
	100	8	75 (50:1)	7:3
Me−≡−Ph	100	75	13[b]	4:1
Ph−≡−Ph	100	75	0	
Et−≡−Et	100	75	0	
Ph−≡−H	100	2	85 (1:3)	50:1

[a] Isolated yield. [b] Only product observed was the hydrazone of phenylacetone. [c] Ratio of E:Z isomers determined by ^1H NMR.

Consequently, we used the reaction of 1,1-dimethylhydrazine with 1-hexyne as the test reaction for catalyst development, which involves the most electron-rich hydrazine used in this study; this is due to the fact that catalysts applicable for reactions involving 1,1-dimethylhydrazine likely will be useful for hydrazines bearing aryl and other groups that decrease the basicity of the substituted nitrogen.

Results of alkyne hydroamination by 1,1-dimethylhydrazine are shown in Tables 1 and 2. Optimization of hydrazine versus alkyne concentration suggested that better yields are obtained when the hydrazine is in slight excess (≥ 1.2 equiv vs alkyne), and reactions were carried out with 3 equiv of 1,1-dimethylhydrazine. All of these preliminary reactions

Table 2. Alkyne Hydroamination by 1,1-Dimethylhydrazine with $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$ (**2**) as Catalyst



alkyne	temp (°C)	time (h)	% yield[a] (Markovnikov:anti-Markovnikov)	E:Z[c]
Bu^n−≡−H	75	24	72 (10:1)	7:3
	100	8	72 (10:1)	4:1
Me−≡−Ph	100	10	92[b]	4:1
Ph−≡−Ph	100	18	22	16:1
Et−≡−Et	100	93	0	
Ph−≡−H	100	2	88 (1:30)	50:1

[a] Isolated yield. [b] Only product observed was the hydrazone of phenylacetone. [c] Ratio of E:Z isomers determined by ^1H NMR.

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(10) Some electron-deficient alkynes react directly with hydrazines. (a) Hamper, B. C.; Kurtzweil, M. L.; Beck, J. P. *J. Org. Chem.* **1992**, *57*, 5680−5686. (b) Tolchinskii, S. E.; Marentina, I. A.; Petrov, A. A. *J. Org. Chem. USSR* **1980**, *16*, 992−998.

(11) For some related transformations, see: (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *Chem. Commun.* **1988**, 121−122. (b) Kauffmann, Th. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 342−361. (c) For the related hydroamination of allene by 1,1-dimethylhydrazine, see ref 8b.

(12) In the titanium dpma system, electronic effects of terminal hydrazido(2−) functional groups and bridging hydrazido(2−) ligands, potential intermediates in the hydroamination catalytic cycle, have been isolated and studied. Li, Y.; Odom, A. L., unpublished results.

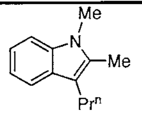
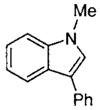
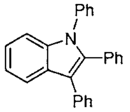
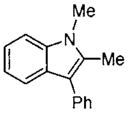
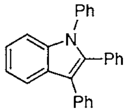
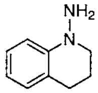
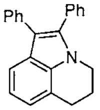
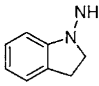
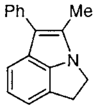
(13) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorg. Chem.* **2001**, *40*, 1987−1988. dpma is *N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine.

(14) (a) Herz, W.; Dittmer, K.; *J. Am. Chem. Soc.* **1947**, *69*, 1698−1700. (b) Kim, H.; Elsenbaumer, R. L. *Tetrahedron Lett.* **1998**, *39*, 1087.

(15) Group IV dap complexes: (a) Huang, J. H.; Chi, L.-S.; Huang, F.-M.; Kuo, P.-C.; Peng, S.-M. *J. Chin. Chem. Soc.* **2000**, *47*, 895−900. (b) Huang, J. H.; Kuo, P.-C.; Lee, G. H.; Peng, S.-M. *J. Chin. Chem. Soc.* **2000**, *47*, 1191−1195. (c) Drevs, H.; Schmeiber, A.; Hartung, H.; Baumeister, U. *Chem. Ber.* **1996**, *129*, 853−857.

(16) A key reaction in the catalysis is likely a [2 + 2] addition of the alkyne to an η^1-hydrazido(2−) intermediate (ref 9). Because the lone pair on the β-nitrogen can donate into the Ti−N π^*-orbital, several resonance forms are possible. A greater donor ability of the β-nitrogen results in a lower Ti−N bond order, which should alter the barrier for the [2 + 2] reaction. For a discussion of η^1-hydrazido(2−) electronics, see: Nugent, W. A.; Mayer, J. M. *Metal−Ligand Multiple Bonds*; Wiley & Sons: New York, 1988.

Table 3. Alkyne Hydroamination by Aryl Hydrazines

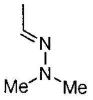
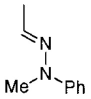
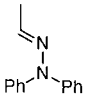
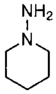
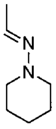
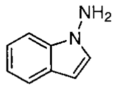
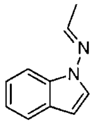
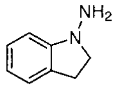
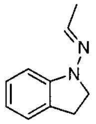
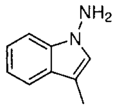
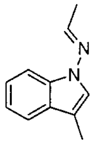
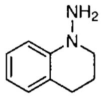
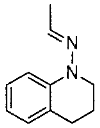
hydrazine	alkyne	time (h)	product	% yield[a]
Ph(Me)NNH_2	Bu^n–≡–H	5		56[b,f]
	Ph–≡–H	18		95[b,f]
	Ph–≡–Ph	48		69[c,f]
	Ph–≡–Me	20		90[d,f]
Ph_2NNH_2	Ph–≡–Ph	48		42[e,g]
	Ph–≡–Ph	40		73[e,f]
	Ph–≡–Me	41		66[d,g]

[a] Yield of purified product. [b] Compound **2** (2 mol %). [c] Compound **1** (2 mol %) . [d] Compound **2** (10 mol %). [e] Compound **1** (10 mol %). [f] After hydrazone generation at 100 °C, 3−5 equiv of $ZnCl_2$ was added, and reaction was heated until conversion was complete. [g] Reaction was carried out at 100 °C, and indole was the only observed product.

were carried out with 10 mol % of the inexpensive and readily prepared precatalysts.

The regioselectivity of the reactions appears to be influenced by alkyne electronics with both catalysts favoring Markovnikov addition to 1-hexyne and anti-Markovnikov addition to phenylacetylene.[18] Hydroamination of internal alkynes was less efficient in general. However, **2** was very effective for 1-phenylpropyne hydroamination and gave modest yields with diphenylacetylene. Neither **1** nor **2** catalyzed 3-hexyne hydroamination with the hydrazines employed. In cases where little or no hydroamination occurred, the alkyne was left unreacted, and no alkyne oligomerization products were observed. The ratios of *E*:*Z* products were obtained by ^1H NMR and are similar to ratios observed when the hydrazones are prepared using 1,1-dimethylhydrazine and carbonyl condensation.

Table 4. Hydroamination of Acetylene by 1,1-Disubstituted Hydrazines

hydrazine	product	% yield[a]
Me_2NNH_2		83
Me(Ph)NNH_2		97
Ph_2NNH_2		99
		86
		95
		96
		95
		94

[a] Isolated yield based on hydrazine. Reactions were carried out in toluene at room temperature. Acetylene was used in excess with 5 mol % **2** as a catalyst.

Reactions involving hydrazines incorporating aryl groups were also investigated (Table 3).[19] A modification of the Fischer indole synthesis[20] occurred in these cases, and substituted indoles were isolated in moderate to high yield.[21]

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(17) For hydroamination involving primary amines, bis(μ-imido) complexes are common intermediates in the catalysis (ref 8). However, the donor ability of the β-nitrogen in hydrazido complexes makes the breakup of the dimeric species to catalytically active monomers more difficult by chelation. For example, catalyses using $Ti(NMe_2)_2$(dpma) are inefficient with H_2NNMe_2 because the bis[μ-hydrazido(2-)] compound is formed irreversibly under the reaction conditions (ref 12).

(18) See ref 9d for a discussion of electronic effects in Group IV metal-catalyzed hydroamination.

(19) Preparation of hydrazines that are not commercially available was accomplished using literature procedures. (a) 1-Aminoindolene and 1-amino-2,3,4-tetrahydroquinoline: Kost, A. N.; Yudin, L. G.; Berlin, Y. A.; Terent'ev, A. P. *Zh. Obshch. Khim.* **1959**, *29*, 3820. (b) 1-Aminoindole and 1-amino-3-methylindole: Somei, M.; Matsubara, M.; Kanda, Y.; Natsume, M. *Chem. Pharm. Bull.* **1978**, *26*, 2522−2534. All other hydrazines were purchased from commercial sources and distilled prior to use.

(20) (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley & Sons: Chichester, UK, 1982. (b) Recent review of indole syntheses: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075.

(21) Hydroamination, usually intramolecular, previously has been used for the generation of indoles. (a) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem.* **2001**, *622*, 149−154. (b) Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chem. Eur. J.* **2000**, *6*, 2513−2522. (c) Burling, S.; Field, L. D.; Messerle, B. A. *Organometallics* **2000**, *19*, 87−90. (d) Tokunaga, M.; Ota, M.; Haga, M.; Wakatsuki, Y. *Tetrahedron Lett.* **2001**, *42*, 3865−3868.

To facilitate indole formation, $ZnCl_2$ was added to some reactions in a one-pot procedure. With diphenylacetylene as a substrate, pyrrolyl catalyst **1** provided the best results. Other reactions were facilitated by the use of thiolate catalyst **2**. All of the indoles listed were readily prepared and isolated on multigram scales using this hydroamination procedure.

Acetylene hydroamination by hydrazines is extraordinarily fast even at room temperature. The hydroaminations were accomplished by simply bubbling acetylene gas at 1 atm through a room-temperature toluene solution of hydrazine and 5 mol % **2**. Regardless of the 1,1-disubstituted hydrazine[19] employed, the reaction was complete in less than 2 h as determined by consumption of the hydrazine starting material and appearance of a new peak in the GC-FID. Some of the reactions were complete after 20 min. Hydrazone products were isolated after purification in $>80\%$ yield for all the hydrazines employed (Table 4).

The scope and mechanism of the reactions are still under investigation, but it is clear that alkyne hydroamination by hydrazines should provide new insights regarding transition metal-mediated C−N bond formation and is a new route to hydrazones, indoles, and related products.

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Supporting Information Available: Synthesis and characterization of compounds **1** and **2**, representative protocols for reaction results in Tables 1−4, and characterization data and literature references for the compounds generated. This material is available free of charge via the Internet at http://pubs.acs.org.

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