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Transition-Metal-Catalyzed Aldehydic C−H Activation by Azodicarboxylates

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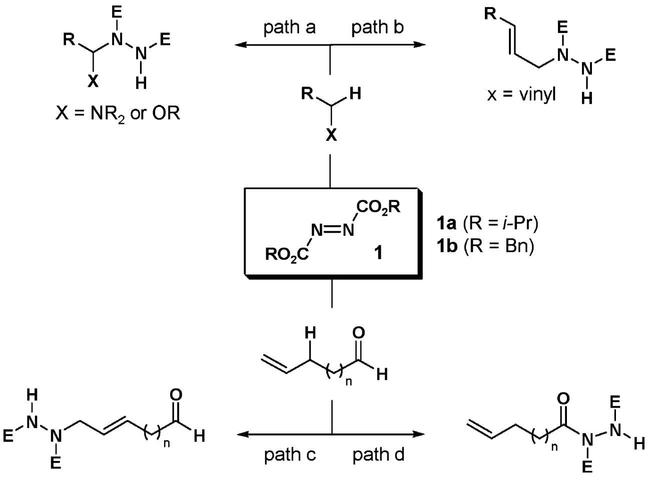
Abstract: Rhodium acetate-catalyzed hydroacylation between aldehydes and an activated form of N=N bond was achieved under mild conditions to provide efficient access to a variety of hydrazino imides. Good selectivity for the aldehydic C−H activation relative to the ene-type reaction was observed with aldehydes having unsaturation both at terminal and internal positions.

Hückel MO theory indicates that the strong electron-withdrawing azodicarboxylates possess a vacant bonding orbital, which predicts these molecules to be good hydrogen and hydride acceptors.[1] With **1**, the C−H activation at the α-position of amines and ethers (path a)[2] and the ene-type reaction (path b)[3] are amply documented. It was also reported that the reaction between **1** and acetaldehyde gave diacetyl under photolytic conditions,[4] whereas Huisgen reported that under thermal conditions[2a] the corresponding addition product (path d) was formed. In our effort to make adducts of unsaturated aldehydes with **1** via "path d", competition between "paths c and d" was noticed. In search for a solution to this problem, we were intrigued by the possibility of accelerating the aldehydic C−H activation (path d) relative to the ene-type reaction (path c) by transition-metal catalysts. Herein, we report a rhodium-catalyzed hydroacylation[5] between a variety of aldehydes and an activated form of N=N bond under mild conditions, thereby providing an efficient synthesis of hydrazino imide functionality with good selectivity between "paths c and d".



For calibration, we first examined the uncatalyzed reaction between hexanal and **1a** in THF at 25 °C. Complete consumption of azodicarboxylate along with the formation of a 1:1 ratio of two major compounds was observed after 3 days. Isolation and characterization of these compounds by ^{1}H NMR, ^{13}C NMR, HRMS, and IR clearly supports the structure of hexanal−**1a** adduct (**2**) and the "path a"-derived THF adduct (**3**). The reaction under neat conditions afforded only **2** but with much reduced reaction rate, requiring 14 days for completion. In search for a catalyst providing higher turnover, we screened various transition-metal catalysts and Lewis acids. Remarkably, within 15 min, complete consumption of **1a** was observed with $[Rh(OAc)_2]_2$ (10 mol %, THF, 25 °C), generating roughly a 1:1 mixture of **2** and the THF adduct **3**. The relative conversion rates of **1a** and hexanal to **2** by other catalysts were also shown in Figure 1. Other than $[Rh(OAc)_2]_2$, only $[RuCl_2(benzene)]_2$ showed significant catalytic activity.[6] Neither Pd complexes nor Lewis acids (EuFOD, $Sm(OTf)_2$, $Sc(OTf)_2$, AgOTf) showed activity higher than background level. Next, we tried different solvents to suppress the formation of a solvent−adduct. When the reaction was carried out in CH_2Cl_2 with $[Rh(OAc)_2]_2$ no reaction occurred. In hexane and toluene, the reaction was much slower. The reactions in Et_2O and 1,4-dioxane gave the expected solvent−adducts **4** and **5**, respectively, but to a lesser extent compared to that in THF; however, in EtOAc, only the desired adduct **2** formed.[7] The amount of catalyst can be as low as 1.5−2.0 mol % without affecting the yield significantly, although the reaction time becomes longer.

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(1) Hückel MO treatment of azodicarbonitrile, see: Marsh, F. D.; Hermes, M. E. *J. Am. Chem. Soc.* **1965**, *87*, 1819. (b) Koga, G.; Anselme, J. P. In *The Chemistry of Hydrazo, Azo, and Azoxy Groups*; Patai, S., Ed.; John Wiley & Sons: New York, 1975; Part 2, p 903.

(2) (a) Diels, O.; Fisher, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 2043. (b) Huisgen, R.; Jakob, F. *Jutus Liebigs Ann. Chem.* **1954**, *590*, 37. (c) Askani, R. *Chem. Ber.* **1965**, *98*, 2551. (d) Cookson, R. C.; Stevens, I. D. R.; Watt, C. T. *Chem. Commun.* **1965**, 259. (e) Smissman, E. E.; Makriyannis, A. *J. Org. Chem.* **1973**, *38*, 1652. (f) Grochowski, E.; Boleskawska, T.; Jurczak, J. *Synthesis* **1977**, 718. (g) Doleschall, G. *Tetrahedron Lett.* **1978**, *19*, 2131. (h) Abarca, B.; Ballesteros, R.; Gonzalez, E.; Sancho, P.; Sepulveda, J.; Soriano, C. *Heterocycles* **1990**, *31*, 1811. (i) Denis, A.; Renou, C. *Tetrahedron Lett.* **2002**, *43*, 4171. In related reactions, alcohols can be oxidized to the corresponding aldehydes and ketones; see: (j) Yoneda, F.; Suzuki, K.; Nitta, Y. *J. Am. Chem. Soc.* **1966**, *88*, 2328. (k) Yoneda, F.; Suzuki, K.; Nitta, Y. *J. Org. Chem.* **1967**, *32*, 727.

(3) For a review, see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1969**, *10*, 1137. (c) Raporterie, A.; Dubac, J.; Lesbre, M. *J. Organomet. Chem.* **1975**, *101*, 187. (d) Stephenson, L. M.; Mattern, D. *J. Org. Chem.* **1976**, *41*, 3614. (e) Jenner, G.; Ben Salem, R. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1961. (f) Leblanc, Y.; Zamboni, R.; Bernstein, M. A. *J. Org. Chem.* **1991**, *56*, 1971. (g) Brimble, M. A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5261. (h) Desimoni, G.; Faita, G.; Righetti, P. P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* **1994**, *50*, 1821. (i) Sarkar, T. K.; Ghorai, B. K.; Das, S.; Grangopadhyay, P.; Rao, S. *Tetrahedron Lett.* **1996**, *37*, 6607.

(4) (a) Schenck, G. O.; Formaneck, H. *Angew. Chem.* **1958**, *70*, 505.

(5) Although it is known that Lewis acids catalyze the ene-type reaction in "path c", catalyzed reactions have not been reported in "path d".

(6) $[Rh(OCOCF_3)_2]_2$ was capable of catalyzing the reaction but found to be much less reactive than $[Rh(OAc)_2]_2$.

(7) The reaction of substrates having slow conversion rate provides varying amounts of the corresponding hydrazodicarboxylate.

10.1021/jo035456o CCC: $27.50

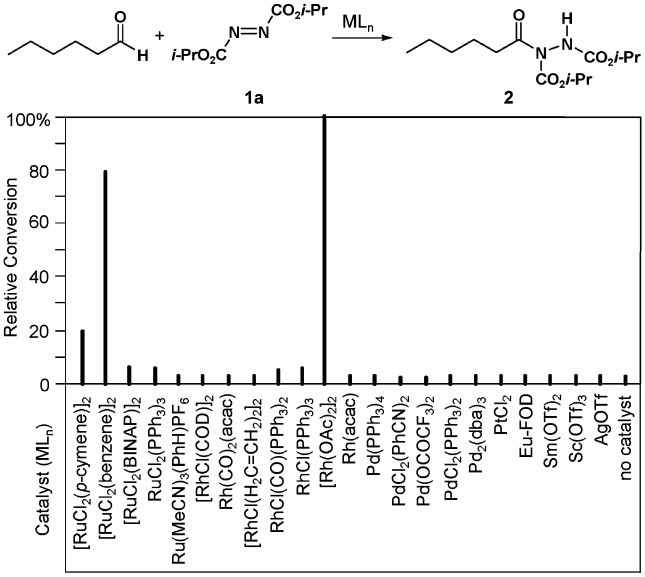
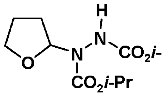


FIGURE 1. Catalyst screening for coupling of hexanal with diisopropyl azodicarboxylate (1). Reactions were performed with 10 mol % catalyst in a 1.0 M solution of 1:1 mixture of hexanal and **1a** in THF at 25 °C. The relative conversion was estimated at the point when the [Rh(OAc)$_2$]$_2$-catalyzed reaction reached to complete consumption of **1a**.



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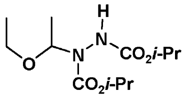

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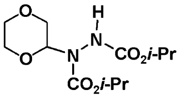

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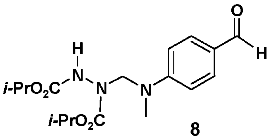
Under the adjusted conditions that balanced the yield and the amount of required catalyst loading (1.5−2.0 mol % of [Rh(OAc)$_2$]$_2$, 1.0 M, EtOAc, 25 °C), **2** was obtained in 84% yield. A variety of aliphatic saturated and unsaturated aldehydes (**6a**−**o**) afforded the expected hydroacylation products (**7a**−**o**) both with **1a** and **1b** in good to excellent yields (Table 1). In general, the reaction became slower as the number of carbons in the substrate aldehyde increased. The unsaturation either at the terminal or internal position does not interfere with the reaction, but in certain cases, the product undergoes ene-type reaction to generate increased amount of bis-azodicarboxylate adduct as the reaction progressed toward completion (entries e, f, and h). An aldehyde (**6c**) with terminal alkyne functionality was also a suitable substrate for this reaction (entry c). Mono- or bis-branched aldehydes (**6e**,**g**,**h**) at either the α- or β-position provided a similar reaction rate and comparable yields (entries e, g, h, and j).



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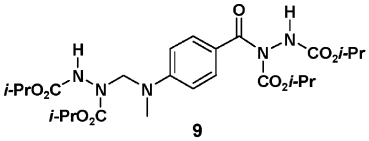

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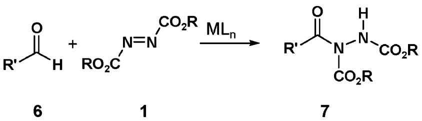
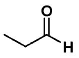
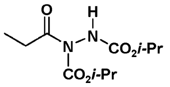
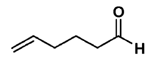
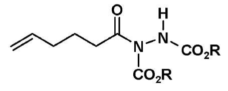
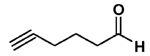
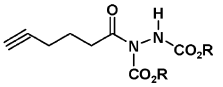
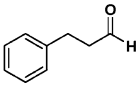
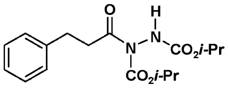
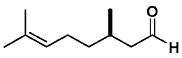
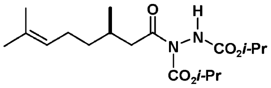
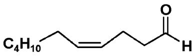
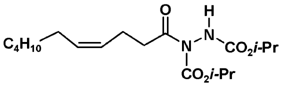
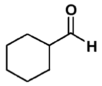
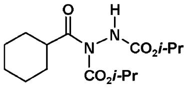
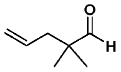
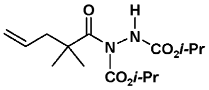
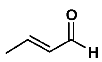
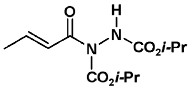
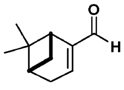
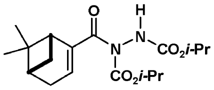
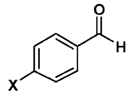
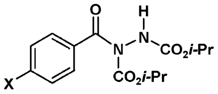
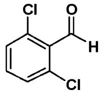
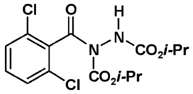
Except for crotonaldehyde (entry i), the reactions of α,β-unsaturated and aromatic aldehydes were much slower, giving incomplete conversion even after a long reaction time. The reaction of aromatic aldehydes with electron-donating substituents was slower (entries k, l), whereas that with electron-withdrawing substituents was faster (entries n, o) than that of the parent benzaldehyde (entry m). In case of 4-dimethylamino benzaldehyde (entry l),

TABLE 1. Hydroacylation of Aldehydes[a]



6 **1** **7**

Entry	Aldehyde	Reaction Time[b] (h)	Hydroacylation Product	Yield (%)
a		12		97
b		24		77 (R = *i*-Pr) 68 (R = Bn)
c		24		74 (R = *i*-Pr) 76 (R = Bn)
d		36		81
e		48		74[c]
f		24		70
g		48		81
h		24		68[c]
i		24		84
j		72		53
				
k	**X = OMe**	120		46
l	**X = NMe$_2$**	120		26[d]
m	**X = H**	120		48
n	**X = Cl**	72		45
o		24		78

[a] Reactions were performed with 1.5−2.0 mol % [Rh(OAc)$_2$]$_2$ with a 1:1 ratio of aldehyde and **1a** or **1b** in EtOAc (1.0 M) at 25 °C. [b] The reaction times were recorded in 12 h increments, and the yields are based on the amount of isolated product. [c] The relatively low yield was caused by the formation of 2:1 adduct of **1a** and aldehyde. [d] The low yield is due to the formation of **8** and **9**.

two additional products were isolated and identified as the C−H activation products **8** and **9**. The formation of these compounds was not unexpected on the basis of the related transformation of compounds with a dimethylamino group as well as the efficient formation of C−H activation products **3**−**5** with ethereal solvents under the same conditions. One intriguing feature of this catalyzed process is that the presence of an aldehyde greatly accelerated the rate of C−H activation at the α-position of ethers and amines.

Mechanistically, the addition of aldehydes to azodicarboxylate was proposed to be a radical-mediated process.[2a,b] This radical mechanism is supported by a complete inhibition of the reaction when it was run with as low as 1 mol % of radical scavenger (4,4′-dithiobis(2,6-di-*tert*-butylphenol).[8] On the other hand, the catalyzed reaction with 10 mol % of $Rh_2(OAc)_4$ proceeded in the presence of 1.0, 2.5, and 5.0 mol % of scavenger, and a complete inhibition was reached at the amount of 10 mol % of the scavenger.[9] On the basis of this observation, it is reasonable to assume that the rhodium-catalyzed version of this reaction may still proceed via radical mechanism although the role of rhodium catalyst is not clear at this point. In a radical mechanism manifold somehow the rhodium catalyst may facilitate the generation or addition of the putative acyl radical[10] intermediate to azodicarboxylate; however, other roles for the catalyst cannot be excluded.[11]

In conclusion, we developed an efficient rhodium-catalyzed hydroacylation reaction between aldehydes and azodicarboxylates. Under these conditions, unsaturated aldehydes give predominantly the hydroacylation product over the ene-type adduct. Further study on the reaction mechanism and the application of this new amide-like bond-forming process is underway.

Acknowledgment. We thank UW−Madison and the Dreyfus Foundation for financial support of this work as well as the NSF and NIH for NMR and Mass Spectrometry instrumentation. We are grateful to Prof. Hans Reich and Prof. Charles Casey for helpful discussions.

Supporting Information Available: Experimental procedures for **2** and **7a**−**o**. Spectral data for **2**−**5** and **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The dependency of the extent of inhibition on the amount of the radical scavenger used in the reaction was pointed out by a reviewer.

[9] Duplicates of both the uncatalyzed and catalyzed reactions were run at 0, 1.0, 2.5, 5.0, and 10 mol % of the scavenger, 4,4′-dithiobis-(2,6-di-*tert*-butylphenol), neat and in 0.2 M solution in EtOAc. The progression of the reaction was monitored by ^1H NMR spectroscopy. The details of this experiment are described in the Supporting Information.

[10] (a) Gottschalk, P.; Neckers, D. C. *J. Org. Chem*. **1985**, *50*, 3498. (b) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 67. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (d) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun*. **2001**, 2352. (e) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem*. **1995**, *48*, 363. (f) Chatgilialoglu, C.; Ferreri, C.; Luarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J.* **1997**, *3*, 376.

[11] The intramolecular trapping experiments of 5-hexenoyl radical derived from 5-hexenal and azodicarboxylate both with and without catalyst were also carried out. In both cases, the formation of 2-methyl cyclopentanone derivative was not observed; instead, only the normal coupled product (**7b**/**7b′**) was isolated in good yield.