Transition Metal Catalyzed Addition of Certain Nucleophiles to Imines

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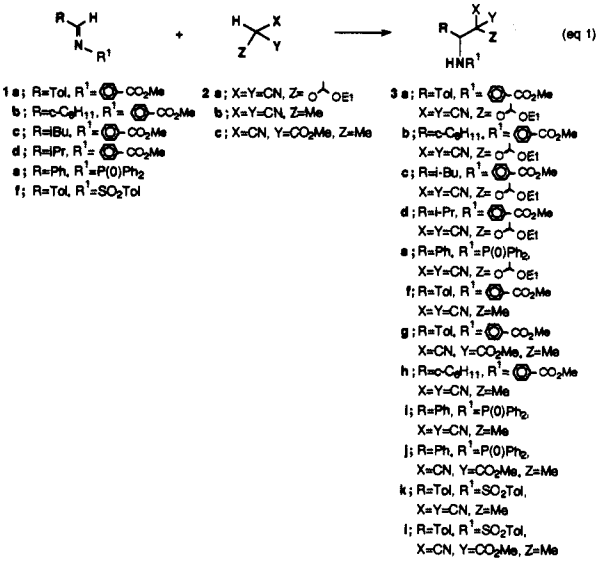
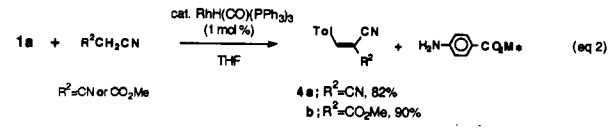
Received January 14, 1994

Transition metal catalyzed asymmetric hydrogenation of imines has been developed in recent years.[1] However, to the best of our knowledge, transition metal catalyzed addition of nucleophiles to imines has not been reported yet,[2] although the ruthenium-catalyzed addition to aldehydes and ketones[3] and ruthenium-[3] and rhodium-catalyzed[4] Michael addition to α,β-unsaturated carbonyl compounds have been reported. We report that imines **1** react with certain nucleophiles **2** in the presence of catalytic amounts of transition metal catalysts under mild reaction conditions to give alkylation products **3** in good yields (eq 1). The results are summarized in Table 1.



Reaction of the Ciufolini imine **1a**[5] with a masked activated formate **2a**[6] was investigated in the presence of several transition metal catalysts. Although Ni(hfacac)$_2$ and Pd(PPh$_3$)$_4$ catalysts gave slightly higher yields than RhHCO(PPh$_3$)$_3$ and Ni(acac)$_2$ catalysts, the reactions in the presence of the former catalysts required cooling (entry 2) or heating (entry 4). Milder reaction conditions are desirable for the preparation of highly functionalized amine derivatives **3**, including masked activated amino acids **3a–e**.[7] Accordingly, we chose RhHCO(PPh$_3$)$_3$ as a representative catalyst. The Ciufolini imines **1b–d** derived from aliphatic aldehydes also gave the coupling products **3b–d** upon treatment with **2a** (entries 5–7). A phosphorus-activated imine **1e**[8] provided **3e** in high yield (entry 8). Not only **2a** but also other nucleophiles (**2b** and **2c**) afforded the corresponding amine derivatives (**3f–l**) in good to high yields (entries 9–17). The reactions of **2b** and **2c** were slow in comparison with that of **2a**, but the use of catalytic amounts of dppe accelerated the condensation reaction. It should be noted that Pd$_2$(dba)$_3$·CHCl$_3$ or La(OiPr)$_3$[9] catalyst is effective for the condensation reaction (entries 10 and 11). The addition products **3k** and **3l** derived from sulfonyl imine **1f** were prone to undergo the reverse reaction to the imine and the nucleophiles (**2b** and **2c**) in the workup process. Accordingly, after the reaction was over (entries 16 and 17), **3k** and **3l** were treated with MOMCl/iPr$_2$NEt in CH$_2$Cl$_2$, and the MOM-protected derivatives were isolated and purified by silica gel column chromatography. When the yield of **3** was low (for example, entries 6 and 7), the starting imine was recovered.

The use of activated imines is essential to the Rh-catalyzed C–C bond formation reaction: ordinary imines such as **1g** (R = R′ = Ph) and **1h** (R = Tol, R′ = Me) did not react with **2a–c** in the presence of the rhodium catalyst. The use of activated nitrile nucleophiles **2** having secondary alkyl chains is also essential to produce **3**: malononitrile (pK_a = 11.2) and methyl cyanoacetate (pK_a > 9) afforded olefins **4** in high yields upon treatment with **1a** (eq 2). Formation of **4** is due to β-elimination of the coupling product **3m** (R = Tol, R^1 = C$_6$H$_4$CO$_2$Me, X = CN, Y = CN or CO$_2$Me, Z = H).[10] The presence of a CN group is more important than the pK_a value of nucleophiles in order to accomplish the C–C bond formation, since dimethyl malonate (pK_a = 13.5) and nitromethane (pK_a = 10.2) are inert to **1a** in the presence of RhH(CO)(PPh$_3$)$_3$.[11]



We next examined asymmetric addition of **2** to **1** by the use of chiral ligands.[4b] All attempts using (*R*)-(+)-BINAP, (+)-norphos, binol, BPPM, BPPFOAc, and TRAP[4b] resulted in failure; at most 10% ee was produced. The low level of asymmetric induction, in comparison with high asymmetric induction in the case of the Michael addition with TRAP,[4b] is presumably due to the fact that chiral discrimination should occur at the imine carbon of **1** whereas it takes place at the nucleophile carbon in the Michael addition. However, a significantly high de was accomplished by using **5a** in which a chiral auxiliary exists at the ester unit. The La(OiPr)$_3$-catalyzed (10 mol %) reaction of **5** with **2b** in THF

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(1) (a) Kang, G. J.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kutney, J. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1466. (b) Ng Cheong Chan, Y.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (c) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558. (d) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002 and references therein. (e) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684. (f) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (g) Willonghby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.

(2) Alkylation of imines with organometallics such as organomagnesium, lithium, zinc, and copper reagents is a well-known reaction. For a review: Kleinmann, E. F.; Volkmann, R. A. In *Comprehensive Organic Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1990; Vol. 2, p 975. Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

(3) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954.

(4) (a) Paganelli, S.; Schionato, A.; Botteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807. (b) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.

(5) Ciufolini, M. A.; Spencer, G. O. *J. Org. Chem.* **1989**, *54*, 4739. We thank Prof. Ciufolini for providing us with a detailed procedure for the preparation of the activated imine.

(6) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515.

(7) The imine **1a** was decomposed slowly at room temperature to the corresponding amine and tolualdehyde in the presence of Ni(hfacac)$_2$; therefore, this catalyst is not suitable for the alkylation of **1a**.

(8) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1987**, 521; **1982**, 270.

(9) Sasaki, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372.

(10) ^{1}H NMR analysis revealed the presence of the coupling product **3m** along with **4** in crude mixtures obtained by allowing the reaction of **1a** with malononitrile in benzene as the solvent to proceed only to low conversion. However, complete β-elimination takes place as the reaction progresses. Elimination also occurred during attempted purification of **3m** by silica gel column chromatography.

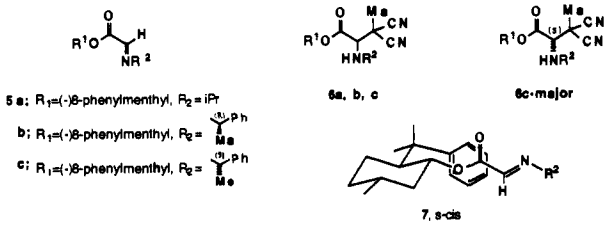
(11) For a mechanistic study of the catalytic aldol type reaction: Hirano, M.; Ito, Y.; Hirai, M.; Fukuoka, A.; Komiya, S. *Chem. Lett.* **1993**, 2057. Mizuho, Y.; Kasuga, N.; Komiya, S. *Chem. Lett.* **1991**, 2127.

0002-7863/94/1516-3161$04.50/0

Table 1. Transition Metal Catalyzed C–C Bond Formation of Imines[a]

entry	imine 1	nucleophile 2	catalyst (mol, %)	react. conditns: temp, time (h), solv	product 3, % yield
1	**1a**	**2a**	$RhHCO(PPh_3)_3$ (3)	rt, 72, THF	**3a**, 75
2	**1a**	**2a**	$Ni(hfacac)_2$ (5)	0 °C, 72, acetone	**3a**, 82
3	**1a**	**2a**	$Ni(acac)_2$ (10)	rt, 72, acetone	**3a**, 71
4	**1a**	**2a**	$Pd(PPh_3)_4$ (10)	50 °C, 24, THF	**3a**, 80
5	**1b**	**2a**	$RhHCO(PPh_3)_3$ (3)	rt, 72, THF	**3b**, 75
6	**1c**	**2a**	$RhHCO(PPh_3)_3$ (3)	rt, 72, THF	**3c**, 49
7	**1d**	**2a**	$RhHCO(PPh_3)_3$ (3)	rt, 72, THF	**3d**, 36
8	**1e**	**2a**	$RhHCO(PPh_3)_3$ (3)	rt, 24, THF	**3e**, 84
9	**1a**	**2b**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 69, THF	**3f**, 91
10	**1a**	**2b**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2), dppe (8)	rt, 42, THF	**3f**, 88
11	**1a**	**2b**	$La(OiPr)_3$ (3)	rt, 42, THF	**3f**, 88
12	**1a**	**2c**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 96, THF	**3g**, 72
13	**1b**	**2b**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 66, THF	**3h**, 88
14	**1e**	**2b**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 48, THF	**3i**, 93
15	**1e**	**2c**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 96, THF	**3j**, 88
16	**1f**	**2b**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 120, THF	**3k**, 99
17	**1f**	**2c**	$RhHCO(PPh_3)_3$ (3), dppe (4)	rt, 120, THF	**3l**, 73

[a] hfacac = $CF_3COCHCOCF_3$; dppe = (diphenylphosphino)ethane; rt = room temperature.



at room temperature gave **6** in 85–93% yields; the diastereoisomer ratios were 92:8 from **5a**, 92:8 from **5b**, and 90:10 from **5c**. Accordingly, the diastereoselectivity was controlled primarily by the chirality of the R^1 rather than the R^2 group. The use of $Pd_2(dba)_3{\cdot}CHCl_3$/4 equiv of dppe or $RhH(CO)(PPh_3)_3$/dppe also produced **6** in high yields with high de. The absolute stereochemistry of the major product from **5c** (**6c**-major) was determined unambiguously by X-ray analysis (see supplementary material); the α-carbon to the amino group possesses the *S* configuration. Accordingly, the nucleophile attacks the imino carbon from the front side of the s-cis conformer **7**, since the back side is blocked by an aromatic ring. We are now in a position to carry out the transition metal catalyzed C–C bond formation of activated imines under essentially neutral conditions at room temperature.[12] Further studies on this new catalyzed reaction are now in progress.

Acknowledgment. We thank Dr. Chizuko Kabuto for the X-ray crystallographic analysis.

Supplementary Material Available: Full spectroscopic characterization of **1**–**6** and crystal data of **6c**-major (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) The reaction of **1a** with **2a** is representative. To a dry THF (1 mL) solution of **1a** (96 mg, 0.38 mmol) and **2a** (88 mg, 0.57 mmol) was added $RhH(CO)(PPh_3)_3$ (15.7 mg, 0.017 mmol) at room temperature, and the mixture was stirred for 72 h. The solvent was removed under reduced pressure, and the product was purified with silica gel column chromatography using hexane–ethyl acetate (10:1) as an eluent. The adduct **3a** was obtained in 75% yield (116 mg, 0.285 mmol) as a colorless oil.