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Lanthanum Isopropoxide Catalyzed Addition of Activated Nucleophiles to Imines

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The addition of certain activated nucleophiles to activated imines is catalyzed by lanthanum isopropoxide. As activated nucleophiles, methylmalononitrile and methyl 2-cyanopropanoate can be utilized. Imines having an electron-withdrawing group either at the carbon or at the nitrogen atom of the C═N double bond can be used; for example *N*-toluenesulfonylimines, *N*-(4-methoxycarbonylphenyl)imines and *α*-imino esters.

Keywords: lanthanum isopropoxide; imines; methylmalonitrile; methyl 2-cyanopropanoate; *α*-imino ester; *N*-toluenesulfonylimine; *N*-(4-methoxycarbonylphenyl)imine; addition to imines

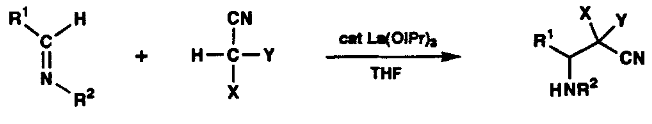
INTRODUCTION

The reactivity of the carbon–nitrogen double bond of imines towards nucleophiles is low in comparison with that of the carbon–oxygen double bond of aldehydes and ketones. To overcome this difficulty, either 'activated' imines (iminium ions)[1-3] or 'activated' nucleophiles[4-6] are frequently used in organic synthesis. As activated nucleophile, $RCu \cdot BF_3$,[5] $R_2CuLi \cdot BF_3$, $RLi \cdot CeCl_3$ and $RMgBr \cdot CeCl_3$ have been utilized,[7] because the alkylation of imines with ordinary organometallic reagents does not proceed in high yield. Most basic (carbanionic) organometallic compounds, such as RMgX and RLi, abstract an *α*-hydrogen from imines, and thus the alkylation is accompanied frequently by a number of side reactions. Accordingly, it is desirable to carry out the alkylation of imines using a non-carbanionic organometallic reagent under essentially neutral conditions. We have reported that transition-metal complexes, such as $RhHCO(PPh_3)_3$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3 \cdot CHCl_3$, (dba = dibenzylideneacetone), catalyze the addition of activated methyne and methylene compounds to imines.[8] As an extension of this study we now report the lanthanum isopropoxide catalyzed addition of activated methyne compounds to imines.

RESULTS AND DISCUSSION

The addition of activated nucleophiles to activated imines was catalyzed by $La(OiPr)_3$ (Eqn [1]). The results are summarized in Table 1.

Reaction of the Ciufolini imine **1** with methyl malononitrile **2** was investigated in the presence of several transition-metal catalysts.[8] Although $Ni(hfacac)_2$ and $Pd(PPh_3)_4$ catalysts gave slightly higher yields than $RhHCO(PPh_3)_3$ and $Ni(acac)_2$ catalysts (hfacac, hexafluoroacetylacetonate; acac, acetylacetonate), the reactions in the presence of the former catalysts required cooling (in the case of the nickel catalyst) or heating. Milder reaction conditions are desirable for the preparation of highly functionalized amine derivatives such as **3**. In this respect, $RhHCO(PPh_3)_3$ or $Pd_2(dba)_3 \cdot CHCl_3$ is more suitable as a transition-metal catalyst since the addition reaction takes place smoothly at room temperature in the presence of these catalysts.



[1]

R¹, R²; electron withdrawing group

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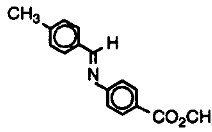
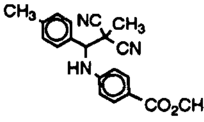
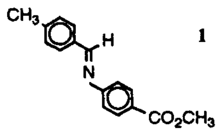
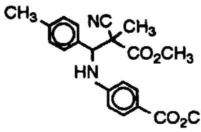
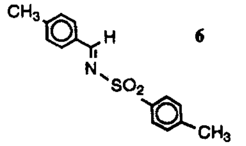
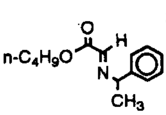
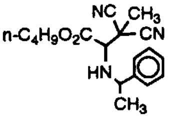
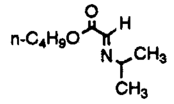
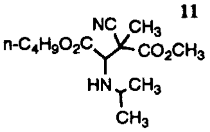
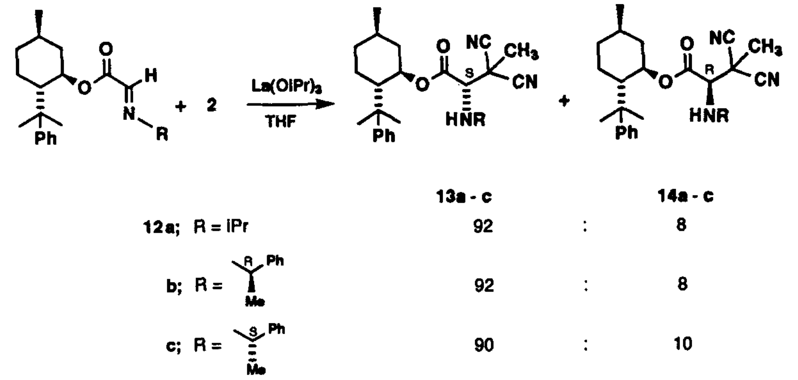
Table 1 La(OiPr)$_3$-catalyzed addition to activated imines[a]

Entry	Imine	Nucleophile	Product	Yield (%)
1	 **1**	$CH_3CH(CN)_2$ **2**	 **3**	88
2	 **1**	$CH_3CH(CN)CO_2CH_3$ **4**	 **5**	60
3	 **6**	$CH_3CH(CN)_2$ **2**	 **7**[b]	72
4	 **8**	$CH_3CH(CN)_2$ **2**	 **9**	94
5	 **10**	$CH_3CH(CN)CO_2CH_3$ **4**	 **11**	84

[a] Racemic 1-phenylethylamine was used for the preparations of **8**. A nearly 1:1 mixture of diastereoisomeric adducts was obtained in entries 2, 4, and 5. [b] Isolated as its MOM-protected derivative.

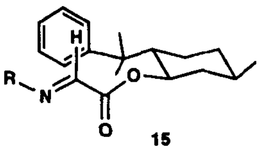
Then we changed the catalyst from the palladium and rhodium complexes to lanthanum isopropoxide La (OiPr)$_3$. The addition reaction proceeded very smoothly to give the corresponding adducts in good to high yields (Table 1). The Ciufolini imine[9] **1** reacted readily with activated methyne compounds **2** and **4** in the presence of 10 mol% La(OiPr)$_3$ (entries 1 and 2). A toluenesulfonyl activated imine **6** provided, upon treatment with **2**, **7** in good yield (entry 3). Compared with the imines **1** and **6** in which an activating group is attached to the nitrogen atom of the C=N double bond, the imine **8** derived from butyl glyoxylate reacted very fast with the activated nucleophiles (entries 4 and 5); normally it took *ca* 24 h for **1** and **6** to complete the reaction, but only a few hours (<3 h) were needed for **8**. Since an electron-withdrawing group is attached to the carbon atom of the C=N double bond, the activation of an imine is accomplished more effectively in the case of **8**.

We next examined asymmetric induction using **12**, in which a chiral auxiliary exists at the ester unit. The La(OiPr)$_3$-catalyzed (10 mol%) reaction of **12** with **2** in THF at room temperature gave a mixture of **13** and **14** in 85–93% yields (Eqn (2)); the diastereoisomer ratios of **13**:**14** were 92:8 from **12a**, 92:8 from **12b**, and 90:10 from **12c**. Accordingly, the diastereoselectivity was controlled primarily by the chirality of the 8-phenylmenthyl group rather than the R group. The absolute stereochemistry of the major product **13c** from **12c** was determined unambiguously by X-ray analysis (Fig. 1). The α-carbon to the



[2]

amino group of **13c** possesses the *S* configuration. Accordingly, the nucleophile attacks the imino carbon from the front side of the *s-cis* conformer **15**, since the back side is blocked by an aromatic ring.



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It is clear that the addition of activated methyne compounds to activated imines proceeds very smoothly in the presence of catalytic amounts of La(OiPr)$_3$, giving the corresponding α-alkylated amines in high yields. The lanthanum isopropoxide method is efficient and convenient for C–C bond formation between activated methynes and imines, and complements the transition-metal catalyzed,[8] high-pressure mediated,[10] or based-induced procedures.[11]

EXPERIMENTAL

All manipulations were carried out under nitrogen or argon. Solvents were dried and distilled. IR spectra were measured on a Hitachi-295

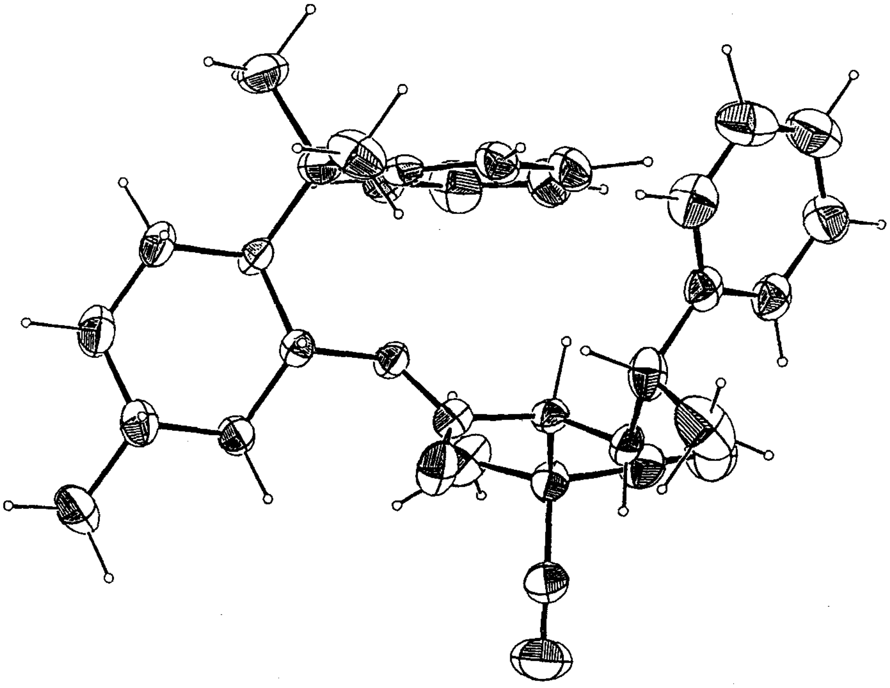

Figure 1 ORTEP drawing of **13c**.

spectrometer. ^{1}H NMR spectra were recorded on a JEOL GSX-270 spectrometer. Microanalyses were performed at the Analytical Center of Tohoku University. The Ciufolini imine **1** was prepared by the literature procedure.[9] The sulfonylimine **6** was prepared according to the Albrecht procedure.[12] The α-imino ester **8** was synthesized by the procedure described in a previous paper.[4] 8-Phenylmenthyl glyoxylate was prepared by the reported procedure,[13] and this aldehyde was converted to the corresponding imines **12a–12c** by the standard procedure. Methylmalononitrile **2** was prepared from methylmalonic acid diethyl ester according to the literature procedure.[14] Methyl 2-cyanopropanoate **4** was prepared from methyl 2-cyanoethanoate upon treatment with NaH followed by MeI.

Typical procedure for the addition reaction of imines: reaction of 1 with 2

To a dry THF (1 ml) solution of **1** (50 mg, 0.198 mmol) and **2** (30 mg, 0.396 mmol) was added La(OiPr)$_3$ (6.1 mg, 10 mol%) under argon, and the mixture was stirred for 24 h. The solvent was removed under reduced pressures and the product was purified with silica gel column chromatography using hexane–ethyl acetate (10:1) as an eluent.

2-Cyano-2-methyl-3-(4-methylphenyl)-3-[*N*-(4-methoxycarbonylphenyl)]aminopropionitrile (3)

Colorless needles, m.p. 106.0–107.5 °C. IR (CHCl$_3$): 3420, 3030, 1715, 1615, 1325, 1440, 1190, 1120 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz): δ 7.85 (d, $J = 8.5$ Hz, 2H, C_6H_4), 7.35 (d, $J = 8.5$ Hz, 2H, C_6H_4), 7.23 (d, $J = 8.5$ Hz, 2H, C_6H_4), 6.67 (*d*, $J = 8.5$ Hz, 2H, C_6H_4), 4.82 (d, $J = 12.0$ Hz, 1H, N*H*), 4.78 (d, $J = 12.0$ Hz, 1H, NHC*H*), 3.84 (s, 3H, CO_2CH_3), 2.35 (*s*, 3*H*, $C_6H_4CH_3$), 1.82 (s, 3H, CCH_3); ^{13}C NMR (CDCl$_3$, 67.5 MHz): δ 166.8, 149.0, 140.2, 131.5, 131.4, 130.0, 127.4, 121.3, 115.3, 114.6, 113.5, 62.7, 51.6, 39.2, 23.3, 21.2.

Analysis: calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.84; H, 5.74; N, 12.67%.

Methyl 2-Cyano-2-methyl-3-(4-methylphenyl)-3-[*N*-(4-methoxycarbonylphenyl)]aminopropionate (5)

Colorless needles, m.p. 138.5–141.5 °C; dec. IR (KBr): ν 3350, 2950, 2160, 1750, 1710, 1605, 1265, 1175, 1105 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz): δ 7.81 and 7.79 (d, $J = 8.5$ Hz, totally 2H, C_6H_4), 7.32 and 7.26 (d, $J = 8.5$ Hz, totally 2H, C_6H_4), 7.17 and 7.14 (d, $J = 8.5$ Hz, totally 2H, C_6H_4), 6.62 and 6.59 (d, $J = 8.5$ Hz, totally 2H, C_6H_4), 5.06 and 4.93 (d, $J = 10.0$ Hz, totally 1H, N*H*), 4.86 and 4.83 (d, $J = 10.0$ Hz, totally 1H, NHC*H*), 3.82 and 3.81 and 3.79 and 3.63 (s, totally 6H, CO_2CH_3), 2.33 and 2.31 (s, totally 3H, $C_6H_4CH_3$), 1.78 and 1.52 (s, totally 3H, CCH_3). ^{13}C NMR (CDCl$_3$, 67.5 MHz): δ 169.2, 168.0, 166.9, 149.8 and 149.5, 139.1 and 139.0, 133.3 and 132.6, 131.5 and 131.4, 129.6, and 129.6, 127.6 and 127.2, 120.3 and 120.3, 118.3 and 118.1, 113.2 and 113.0, 61.9 and 61.5, 54.0 and 53.6, 51.6, 51.1 and 50.6, 22.0 and 21.5, 21.2.

Analysis: calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.68; H, 6.14; N, 7.54%.

The adduct **7** was prone to undergo the back reaction to the starting imine **6** upon treatment with the silica gel column. The retro-reaction was prohibited by converting the adduct to the corresponding methoxymethyl- (MOM-) protected derivative **16**.

2-Cyano-2-methyl-3-(4-methylphenyl)-3-[*N*-(4-methylphenylsulfonyl)-*N*-(methoxymethyl)]-aminopropionitrile (16)

Colorless oil. IR (KBr): ν 3030, 2985, 2950, 2260, 2160, 1620, 1600, 1524, 1500, 1464, 1356, 1182, 1068, 1036, 978, 934, 908, 846, 836, 822 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz): δ 7.65 (d, $J = 8.1$ Hz, 2H, C_6H_4), 7.33 (d, $J = 8.1$ Hz, 2H, C_6H_4), 7.24 (d, $J = 8.1$ Hz, 2H, C_6H_4), 7.13 (d, $J = 8.1$ Hz, 2H, C_6H_4), 5.32 (s, 1H, CHN), 4.85 (d, $J = 11.0$ Hz, 1H, OCH_2N), 4.68 (d, $J = 11.0$ Hz, 1H, OCH_2N), 3.30 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3Ph), 2.33 (s, 3H, CH_3Ph), 1.90 (s, 3H, $CH_3C(CN)_2$). High-resolution MS (HRMS): *m/z* calcd for $C_{21}H_{23}N_3O_3S$ (M^+) 397.1460; found 397.1466.

Butyl 3,3-dicyhano-2-*N*-(1-phenylethyl)aminobutyrate (9)

Colorless oil. IR (CCl$_4$): ν 3325, 3100, 3075, 3040, 2975, 2875, 1740, 1450, 1200, 700 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) [major product]: δ 7.2–7.4 (m, 5H), 3.9–4.3 (m, 2H), 3.79 (q, 1H, $J = 6.5$ Hz), 3.54 (br s, 1H), 2.55 (br s, 1H), 1.79 (s, 3H), 1.56 (m, 2H), 1.43 (d, 3H, $J = 6.5$ Hz), 1.29 (m, 2H), 0.97 (t, 3H, $J = 7.0$ Hz). [Minor product]: δ 7.2–7.4 (m, 5H), 3.79 (q, 1H, $J = 6.5$ Hz), 3.25 (br s, 1H), 2.30 (br s, 1H), 1.70 (s, 3H), 1.50 (m, 2H), 1.41 (d, 3H, $J = 6.5$ Hz), 1.29 (m, 2H), 0.89 (t, 3H, $J = 7.0$ Hz).

Analysis: calcd for $C_{13}H_{21}N_2O_3$: C, 62.13; H, 8.42; N, 16.71. Found: C, 61.99; H, 8.42; N, 16.72%.

Butyl 3-cyano-2-*N*-isopropylamino-3-methoxycarbonylbutyrate (11)
Colorless oil. IR (neat): ν 3350, 2970, 2890, 2260, 1740, 1460, 1270 cm^{-1}. ^{1}H NMR: δ 4.19 and 4.195 (t, totally 2H, $J = 6.5$ Hz), 3.83 and 3.84 (s, totally 3H), 3.72 (d, 1H, $J = 10$ Hz), 2.76 and 2.86 (sept, totally 1H, $J = 6.0$ Hz), 1.95 (br s, 1H), 1.65 (m, 2H), 1.57 and 1.64 (s, totally 3H), 1.41 (m, 2H), 0.98 and 1.20 (t, totally 3H, $J = 6.0$ Hz), 0.93 and 1.70 (d, totally 6H, $J = 6.0$ Hz).

Analysis: calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 58.81; H, 8.42; N, 9.65%.

(−)-8-Phenylmenthyl 3,3-dicyano-2-*N*-isopropylaminobutyrate (13a)
Colorless oil. IR (neat): ν 3340, 3100, 3075, 3030, 2990, 2950, 2890, 1740, 1605, 1230, 780, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) [major product]: δ 7.15–7.35 (m, 5H), 4.86 (td, 1H, $J = 11.0$, 4.0 Hz), 2.62 (sept, 1H, $J = 6.0$ Hz), 2.44 (br s, 1H), 2.27 (ddd, 1H, $J = 12.0$, 11.0, 3.5 Hz), 1.90 (m, 2H), 1.70 (m, 2H), 1.54 (s, 3H), 1.30 (s, 3H), 1.19 (s, 3H), 1.05 (d, 3H, $J = 6.0$ Hz), 1.01 (d, 3H, $J = 6.0$ Hz), 0.90 (d, 3H, $J = 6.0$ Hz).

Analysis: calcd for $C_{21}H_{31}NO_2$: C, 73.31; H, 8.61; N, 10.26. Found: C, 73.13; H, 8.73; N, 10.09%.

(−)-8-Phenylmenthyl 3,3-dicyano-2-*N*-[(*R*)-1-phenylethyl]aminobutyrate (13b)
Colorless oil. IR (CCl_4): ν 3360, 3075, 3045, 2990, 2945, 1745, 1610, 1440, 1385, 1310, 1235, 715 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) [major product]: δ 7.2–7.5 (m, 5H), 7.0–7.2 (m, 3H), 6.9–7.0 (m, 2H), 4.76 (td, 1H, $J = 10.5$, 4.5 Hz), 3.84 (q, 1H, $J = 6.7$ Hz), 2.79 (s, 1H), 2.6–2.8 (br s, 1H), 2.08 (td, 1H, $J = 11.5$, 3.5 hz), 1.90 (br d, 1H, $J = 12.0$ Hz), 1.76 (dq, 1H, $J = 13$, 3.5 Hz), 1.66 (br, d, 1H, $JI = 13$ Hz), 1.48 (s, 3H), 1.37 (d, 3H, $J = 6.7$ Hz); 1.05 (s, 3H), 0.98 (s, 3H), 0.88 (d, 3H, $J = 6.4$ Hz), 0.8–1.6 (m, 4H). [Minor product]: δ 7.1–7.4 (m, 9H), 6.97 (tt, $J = 7.0$, 1.2 Hz), 4.97 (td, 1H, $J = 10.5$, 4.3 Hz), 3.79 (q, 1H, $J = 6.6$ Hz), 2.45 (s, 1H), 2.16 (ddd, 1H, $J = 12.0$, 10.5, 3.6 Hz), 2.04 (br d, 1H, $J = 12$ Hz), 1.53 (s, 3), 1.32 (s, 3H), 1.23 (s, 3H), 0.93 (d, 3H, $J = 6.2$ Hz), 0.8–1.9 (m, 10H).

Analysis: calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.34; H, 7.91; N, 8.94%.

(−)-8-Phenylmenthyl 3,3-dicyano-2-*N*-[(*S*)-1-phenylethyl]aminobutyrate (13c)
Colorless crystals, m.p. 150.5–152.5 °C. IR (KBr): ν 3325, 3100, 3070, 3050, 2975, 2940, 2900, 2850, 2170, 1740, 1600, 1210, 770, 710 cm^{-1}: ^{1}H NMR ($CDCl_3$, 270 MHz) [major product]: δ 6.9–7.4 (m, 10H), 3.63 (q, 1H, $J = 6.0$ Hz), 2.66 (br s, 1H), 1.38 (s, 3H), 1.32 (d, 3H, $J = 6.0$ Hz), 1.19 (s, 3H), 1.13 (s, 3H), 0.83 (d, 3H, $J = 6.0$ Hz), 0.8–2.2 (m, 8H). [Minor product]: δ 6.9–7.4 (m, 10H), 3.63 (q, 1H, $J = 6.0$ Hz), 2.46 (br s, 1H), 1.38 (s, 3H), 1.32 (d, 3H, $J = 6.0$ Hz), 1.19 (s, 3H), 1.13 (s, 3H), 0.83 (d, 3H, $J = 6.0$ Hz); 0.8–2.2 (m, 8H).

Analysis: calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.34; H, 7.91, N, 8.94%.

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