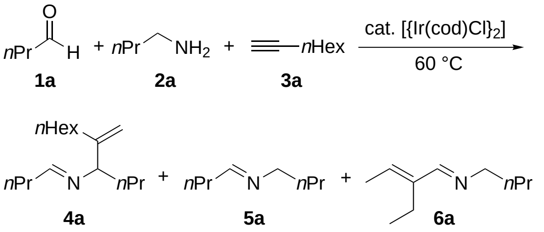
[9] a) M. Pecul, J. Leszczynski, J. Sadlej, *J. Phys. Chem. A* **2000**, *104*, 8105; b) M. Pecul, J. Leszczynski, J. Sadlej, *J. Chem. Phys.* **2000**, *112*, 7930.
[10] W. D. Arnold, J. Mao, H. Sun, E. Oldfield, *J. Am. Chem. Soc.* **2000**, *122*, 12164.
[11] A. Bagno, *Chem. Eur. J.* **2000**, *6*, 2925.
[12] F. R. Salsbury, R. A. Harris, *Mol. Phys.* **1998**, *94*, 307.
[13] M. Nishio, M. Hirota, Y. Umezawa, *The CH/π Interaction, Evidence, Nature and Consequences*, Wiley-VCH, New York, NY, **1998**.
[14] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[15] T. H. Dunning, *J. Chem. Phys.* **1987**, *98*, 1007.
[16] S. Tsuzuki, T. Uchimaru, M. Mikami, K. Tanabe, *Chem. Phys. Lett.* **1996**, *252*, 206.
[17] S. Tsuzuki, K. Tanabe, *J. Phys. Chem.* **1991**, *95*, 2272.
[18] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.
[19] a) D. R. Salahub, R. Fournier, P. Mlynarski, I. Papai, A. St-Amant, J. Ushio in *Density Functional Methods in Chemistry* (Eds.: J. Labanowski, J. Andzelm), Springer, New York, NY, **1991**; b) A. St-Amant, D. R. Salahub, *Chem. Phys. Lett.* **1990**, *169*, 387; c) V. G. Malkin, O. L. Malkina, M. E. Casida, D. R. Salahub, *J. Am. Chem. Soc.* **1994**, *116*, 5898; d) V. G. Malkin, O. L. Malkina, L. A. Eriksson, D. R. Salahub, *Modern Density Functional Theory: A Tool For Chemistry*, *Vol. 2* (Eds.: J. M. Seminario, P. Politzer), Elsevier, Amsterdam, **1995**; e) V. G. Malkin, O. L. Malkina, D. R. Salahub, *Chem. Phys. Lett.* **1994**, *221*, 91; f) O. L. Malkina, D. R. Salahub, V. G. Malkin, *J. Chem. Phys.* **1996**, *105*, 8793.
[20] T. Helgaker, M. Watson, N. C. Handy, *J. Chem. Phys.* **2000**, *113*, 9402.
[21] S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200.
[22] W. Kutzelnigg, U. Fleischer, M. Schindler, *NMR—Basic Principles and Progress*, *Vol. 23*, Springer, Berlin, **1990**.
[23] A. Bagno, *Chem. Eur. J.* **2001**, *7*, 1652–1661.
[24] W. Xu, R. J. Puddephatt, L. Manojlovic-Muir, K. W. Muir, C. S. Frampton, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 277.
[25] *Handbook of Chemistry and Physics*, 69th ed., CRC, Boca Raton, FL, **1988–1989**.
[26] C. Adamo, V. Barone, *J. Chem. Phys.* **1998**, *108*, 664.
[27] K. Burke, J. P. Perdew, Y. Wang in *Electronic Density Functional Theory: Recent Progress and New Directions*, (Eds.: J. F. Dobson, G. Vignale, M. P. Das), Plenum Press, New York, NY, **1998**.
[28] P. L. Anelli, P. R. Ashton, R. Ballardini, V. Balzani, M. Delgado, M. T. Gandolfi, T. T. Goodnow, A. E. Kaifer, D. Philp, M. Pietraszkiewicz, L. Prodi, M. V. Reddington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, C. Vincent, D. J. Williams, *J. Am. Chem. Soc.* **1992**, *114*, 193.

A Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes

Satoshi Sakaguchi, Takashi Kubo, and Yasutaka Ishii*

Since the decisive breakthrough in 1993 by Murai et al., who achieved a highly efficient ruthenium-catalyzed addition of aromatic C–H bonds to olefins,[1] carbon–carbon bond formation through the activation of C–H bonds by transition metal complexes is recognized as a new category of chemistry.[2, 3] So far there have been a number of cases of C–C bond formation through activation of the C–H bond adjacent to the heteroatom.[3–5] Recently, it was shown that some iridium complexes cleave the C–H bond of nitriles[6] or 1-naphthols[7] to provide a new C–C bond. To the best of our knowledge, however, no reports have appeared on C–C bond formation by the activation of C–H bonds neighboring the nitrogen atom of imines. In continuation of our studies on iridium-catalyzed reactions of imines,[8] we have now found a new type of C–H bond activation adjacent to the nitrogen atom of imines by an iridium complex, leading to a three-component coupling reaction of aldehydes, amines, and alkynes.

The reaction of *n*-butyraldehyde (**1a**), *n*-butylamine (**2a**), and 1-octyne (**3a**) was selected as a model reaction and examined in the presence of a catalytic amount of $[\{Ir(cod)Cl\}_2]$ (cod = cycloocta-1,5-diene) under various reaction conditions [Eq. (1), Table 1]. To a solution containing $[\{Ir(cod)Cl\}_2]$ in THF was added a 1:1:1 mixture of **1a**, **2a**, and **3a**. The reaction was carried out with stirring at 60 °C for 15 h, giving the coupling products *N*-butyliden(2-hexylpropylallyl)amine (**4a**), imine **5a**, and *α*,*β*-unsaturated imine **6a** in 57%, 28% and 11% yields, respectively (Table 1, run 1). When two equivalents of **1a** and **3a** with respect to **2a** were employed, **4a** was formed in higher yield (72%, run 2). Interestingly, the reaction took place at 50 °C to give **4a** in moderate yield (56%, run 4), although the usual catalytic addition of C–H bonds to alkenes and alkynes calls for higher reaction temperatures (> 100 °C).[1–5] When the reaction was terminated after 7 h, a considerable amount of imine **5a** remained unchanged (run 5). This shows that the reaction is



(1)

---

[*] Prof. Y. Ishii, S. Sakaguchi, T. Kubo
Department of Applied Chemistry
Faculty of Engineering & High Technology Research Center
Kansai University
Suita, Osaka 564-8680 (Japan)
Fax: (+81) 6-6339-4026
E-mail: ishii@ipcku.kansai-u.ac.jp

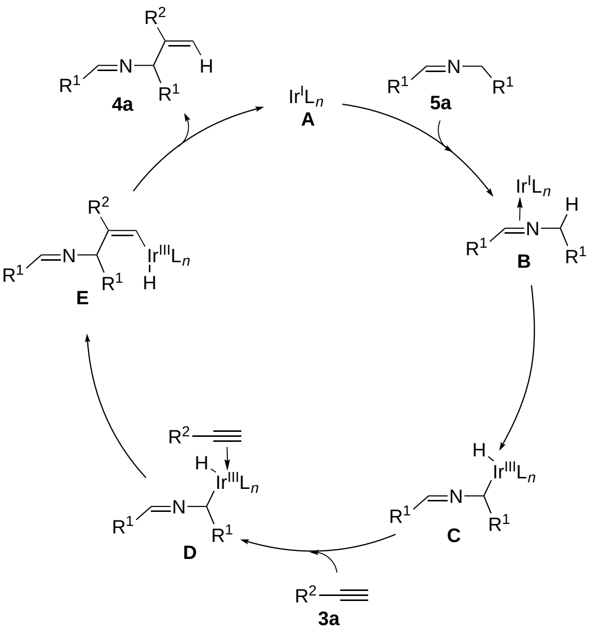
Table 1. Results of the three-component coupling reaction of *n*-butyraldehyde (**1a**), *n*-butylamine (**2a**), and 1-octyne (**3a**) catalyzed by [{Ir(cod)Cl}$_2$] under various conditions [Eq. (1)].[a]

Run	Solvent	Yield [%][b]		
		4a	**5a**	**6a**
1[c]	THF	57	28	11
2	THF	72	7	12
3[d]	THF	48	8	16
4[e]	THF	56	13	12
5[f]	THF	54	32	10
6[g]	THF	68	3	18
7[h]	THF	49	13	15
8[i]	THF	0	2	40
9	DME	64	7	8
10	toluene	53	11	13
11	EtOH	9	26	34

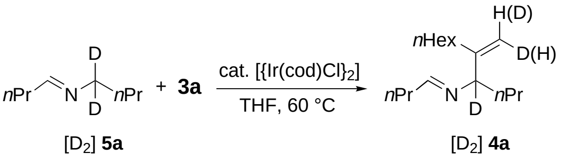
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), **3a** (0.5 mmol), [{Ir(cod)Cl}$_2$] (0.025 mmol), solvent (2 mL), 60 °C, 15 h. [b] Yield based on amount of **2a** used. [c] As in [a], except: **1a** (0.25 mmol), **3a** (0.25 mmol). [d] As in [a], except: THF (1 mL). [e] As in [a], except: 50 °C. [f] As in [a], except: 7 h. [g] Compound **5a** (0.25 mmol) was allowed to react with **3a** (0.5 mmol) under the same reaction conditions as run 2. [h] Catalyst: [{Ir(cyclooctene)$_2$Cl}$_2$] (0.025 mmol). [i] Catalyst: IrCl$_3$ (0.025 mmol).

initiated by the reaction of **1a** with **2a**, leading to the imine **5a**. Indeed, the reaction of imine **5a** with **3a** under the influence of the Ir complex in THF gave **4a** in satisfactory yield (run 6). The catalytic activity of [{Ir(cyclooctene)$_2$Cl}$_2$] was lower than that of [{Ir(cod)Cl}$_2$], and IrCl$_3$ was inert (runs 7 and 8). Among the solvents examined, THF was found to be the best, followed by DME and toluene. A protic solvent like EtOH promoted an aldol-type reaction of imine **5a** to **6a** rather than the coupling reaction (runs 9–11).

The reaction shown in Equation (1) seems to proceed through the following reaction path (Scheme 1): First, the Ir^I complex **A** coordinates to **5a**, which is generated in situ from aldehyde **1a** and amine **2a**. Oxidative addition of the Ir^I center at the C–H bond adjacent to the nitrogen atom in **5a** affords Ir^{III} complex **C**. Coordination of alkyne **3a** followed by insertion in complex **D** gives iridium complex **E**, and subsequent reductive elimination forms the coupling product **4a**. To obtain further insight into the reaction pathway, the reaction of *N*-butyliden-1,1-dideuteriobutylamine ([D$_2$]**5a**), prepared independently, with **3a** under the influence of [{Ir(cod)Cl}$_2$] was examined [Eq. (2)]. As expected the coupling product [D$_2$]**4a**, in which a deuterium atom is incorporated at the terminal triple bond of **3a**, was produced. It is noteworthy that [D$_2$]**4a** consisted of a single geometrical isomer. This shows that the present coupling reaction takes place with high stereoselectivity, although it is not clear where the stereochemistry comes from.



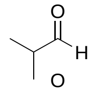
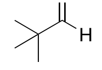
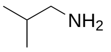
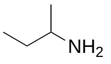
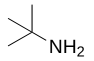
Scheme 1. A possible reaction path for the three-component reaction. R^1 = *n*Pr, R^2 = *n*Hex; L$_n$ = ligand.



(2)

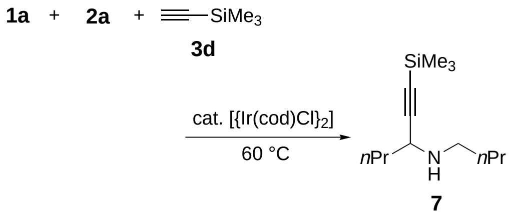
On the basis of these results, the three-component coupling reactions of several different aldehydes, amines and alkynes were examined (Table 2). In most cases the reactions produced the corresponding coupling products in fair to good yields (runs 1, 3–6). The reaction with the internal alkyne 4-octyne (**3c**) did not form a three-component coupling product, but instead **5a** and **6a** (run 2). Needless to say, no coupling reaction took place upon use of *tert*-butylamine, which has no α-hydrogen atom (run 7). The reaction of benzaldehyde or crotonaldehyde or 2-octanone with **2a** and **3a** is unfortunately difficult to carry out under these conditions. Finally, almost no reaction took place upon treatment of 2-aminoethanol or allyl amine with **1a** and **3a**.

Table 2. Results of the three-component coupling reaction of various aldehydes, amines, and alkynes catalyzed by [{Ir(cod)Cl}$_2$].[a]

Run	Aldehyde	Amine	Alkyne	Yield [%] of **4**
1	**1a**	**2a**	≡—*n*Bu **3b**	74
2	**1a**	**2a**	*n*Bu—≡—*n*Bu **3c**	0[b]
3	 **1b**	**2a**	**3a**	73
4	 **1c**	**2a**	**3a**	62
5	**1a**	 **2b**	**3a**	60
6	**1a**	 **2c**	**3a**	45
7	**1a**	 **2d**	**3a**	0

[a] The aldehyde (0.5 mmol), amine (0.25 mmol), and alkyne (0.5 mmol) were allowed to react in THF (2 mL) in the presence of a catalytic amount of [{Ir(cod)Cl}$_2$] (0.025 mmol) at 60 °C for 15 h. [b] Compounds **5a** (83 %) and **6a** (4 %) were obtained.

The reaction of **1a**, **2a**, and trimethylsilylacetylene (**3d**) under the influence of [{Ir(cod)Cl}$_2$] afforded an adduct, butyl(1-propyl-3-trimethylsily-2-propynyl)amine [**7**; Eq. (3)].



(3)

Here the the alkyne **3d** has added to the double bond of the imine **5a** initially formed, in contrast to the reaction of the aliphatic alkyne **3a**. It is probable that the reaction proceeds through the oxidative addition of the Ir^I complex to the terminal C–H bond of alkyne **3d**, followed by insertion of the imine to the resulting Ir–H complex. Recently, Miyaura et al. reported that the iridium-catalyzed dimerization of terminal alkynes involves the oxidative addition of a low-valent Ir complex to alkyne, followed by insertion of an alternative alkyne to give dimers.[9]

In summary, we have developed a new reaction of aldehydes, amines, and alkynes catalyzed by an Ir complex to produce three-component coupling products. These products are difficult to obtain by conventional organic synthetic methods.

Experimental Section

Representative procedure: The aldehyde (0.5 mmol), amine (0.25 mmol), and alkyne (0.5 mmol) were added under Ar to a solution of [{Ir(cod)Cl}$_2$] (0.025 mmol) in THF (2.0 mL). Then the reaction mixture was stirred at 60 °C for 15 h. The reaction was quenched with wet Et$_2$O, and the products were isolated by column chromatography (230–400 mesh Al$_2$O$_3$, hexane) and purified by distillation under reduced presure. After the reaction, GC and GC-MS analyses were performed. The yields of the products were estimated from the peak areas based on the internal standard technique using GC.

4a: ^{1}H NMR: $\delta = 7.59$ (t, $J = 4.9$ Hz, 1H), 4.91 (s, 1H), 4.76 (d, $J = 1.3$ Hz, 1H), 3.41 (t, $J = 6.9$ Hz, 1H), 2.25 (dt, $J = 5.3$, 7.3 Hz, 2H), 2.04 (t, $J = 7.3$ Hz, 2H), 1.65–1.09 (m, 14H), 0.95 (t, $J = 7.6$ Hz, 3H), 0.88 (t, $J = 4.6$ Hz, 6H); ^{13}C NMR: $\delta = 163.8$, 151.7, 108.9, 76.0, 37.6, 36.7, 32.5, 31.7, 29.1, 27.7, 22.5, 19.6, 14.0, 13.8, 13.7; IR (neat) 2957, 1667, 1462, 897 cm^{-1}; MS (70 ev) *m*/*z* (%): 237 (0.3) [M^+], 194 (100), 180 (5), 166 (16).

7: ^{1}H NMR: $\delta = 3.35$ (dd, $J = 7.7$, 5.9 Hz, 1H), 2.84 (ddd, $J = 6.6$, 8.4, 11.4 Hz, 1H), 2.56 (ddd, $J = 5.9$, 8.0, 11.4 Hz, 1H), 1.61–1.33 (m, 8H), 0.94 (t, $J = 7.3$ Hz, 3H), 0.91 (t, $J = 7.3$ Hz, 3H), 0.16 (s, 9H); ^{13}C NMR: $\delta =$ 100.2, 87.3, 50.6, 47.0, 38.0, 32.1, 20.4, 19.2, 13.9, 13.8, 0.1; IR (neat) 3299, 2959, 2159, 1458, 1243, 842 cm^{-1}; MS (70 ev) *m*/*z* (%): 182 (100), 109 (4), 73 (12).

Received: February 26, 2001 [Z16687]

---

[1] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529–531.

[2] S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225–233; G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; A. Sen, *Acc. Chem. Res.* **1998**, *31*, 550–557; A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154–162; A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403–424.

[3] *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, New York, **1999**; N. Chatani, T. Fukuyama, H. Tatamidani, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, *65*, 4039–4047; Y. Ie, N. Chatani, T. Ogo, D. R. Marshall, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, *65*, 1475–1488, and references therein; K. Kokubo, K. Matsumasa, Y. Nishinaka, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303–311, and references therein.

[4] *Activation and Functionalization of Alkanes* (Ed.: C. L. Hill), Wiley, New York, **1989**; C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263; H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070; H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, *287*, 1995–1997.

[5] D. M. Tellers, R. G. Bergman, *J. Am. Chem. Soc.* **2000**, *122*, 954–955; F. Torres, E. Sola, M. Martín, J. A. López, F. J. Lahoz, L. A. Oro, *J. Am. Chem. Soc.* **1999**, *121*, 10632–10633; S. Niu, M. B. Hall, *J. Am. Chem. Soc.* **1998**, *120*, 6169–6170; J. C. W. Lohrenz, H. Jacobsen, *Angew. Chem.* **1996**, *108*, 1403–1405; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1305–1307; B. A. Arndtsen, R. G. Bergman, *Science* **1995**, *270*, 1970–1973.

[6] H. Takaya, T. Naota, S.-I. Murahashi, *J. Am. Chem. Soc.* **1998**, *120*, 4244–4245.

[7] T. Satoh, Y. Nishinaka, M. Miura, M. Nomura, *Chem. Lett.* **1999**, 615–616.

[8] T. Kubo, S. Sakaguchi, Y. Ishii, *Chem. Commun.* **2000**, 625–626.

[9] T. Ohmura, S.-I. Yorozuya, Y. Yamamoto, N. Miyaura, *Organometallics* **2000**, *19*, 365–367.

Unprecedented Detection of Distinct Barriers Involving Formally Enantiotopic Substituents: Phenyl Rotation in Solid Diphenyl Sulfoxide**

Daniele Casarini,* Lodovico Lunazzi,* and
Andrea Mazzanti

It has been pointed out that "the vast majority of molecules are chiral, not achiral; to realize it, one only needs a sufficiently fine spatial or temporal resolution of measurement".[2] To illustrate this point herein, we refer to the recent observation that dimesityl sulfoxide (Mes$_2$S=O; Mes = 2,4,6-trimethylphenyl), which by convention is an achiral molecule

---

[*] Prof. D. Casarini
Dipartimento di Chimica, Università della Basilicata
Via N. Sauro, 85, Potenza, 85100 (Italy)
Fax: (+39) 0971 202 223
E-mail: casarini@unibas.it

Prof. L. Lunazzi, Dr. A. Mazzanti
Dipartamento di Chimica Organica "A. Mangini"
Università di Bologna
Risorgimento, 4, Bologna, 40136 (Italy)
Fax: (+39) 051-209-3654
E-mail: lunazzi@ms.fci.unibo.it

[**] Conformational Studies by Dynamic NMR. Part 82. For Part 80 see ref. [1a], for Part 81 see ref. [1b]. We thank J. E. Anderson (University College, London, UK), S. E. Biali (Hebrew University, Jerusalem, Israel), R. K. Harris (University of Durham, UK), W. B. Jennings (University College, Cork, Ireland), A. Rassat (École Normale Superieure, Paris, France) for critical reading of the manuscript, and I.Co.C.E.A., CNR, Bologna for access to the 400-MHz and solid-state NMR spectroscopy facilities. Financial support was received from MURST (national project "Stereoselection in Organic Synthesis") and from the University of Bologna (Funds for selected research topics 1999–2001).