When the emission spectra of the CPFs in methanol (10% sodium phosphate buffer) excited at 370 nm were detected, the emission of the fluorescein acceptor could be observed in all CPFs. The hydrophobic interaction between the fluorophores would be weaker in methanol than in aqueous solution and the fluorophores may not come into close contact in organic solvents. When the absorption spectra of CPFs in methanol were detected, the red shift of the absorption spectra observed in aqueous solution was not observed, indicating that the two fluorophores did not come into close contact. This result indicates that, in methanol, the hydrophobic interaction between the fluorophores is weakened and the emission of the acceptor caused by RET can be observed.

In conclusion, we have shown that in designing a RET probe for ratiometric measurements, it is possible to observe the emission of the acceptor if the structure of the probe is such as to prevent close contact of the two fluorophores.

Received: April 11, 2000 [Z14974]

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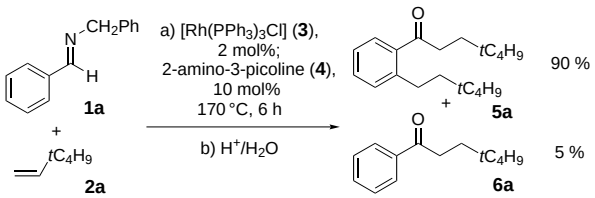
The Catalytic Alkylation of Aromatic Imines by Wilkinson's Complex: The Domino Reaction of Hydroacylation and *ortho*-Alkylation**

Chul-Ho Jun,* Jun-Bae Hong, Yeon-Hee Kim, and Kwan-Yong Chung

Transition metal catalyzed C–H bond activation and the subsequent coupling of the organic fragment to an olefin is a promising area in which to find a convenient method for the construction of a carbon skeleton.[1] We have studied C–H bond activation through the hydroacylation of olefins using aldehydes, alcohols, and aldimines.[2, 3] Unexpectedly during our experiments on transimination-assisted hydroacylation with aldimines,[3] *ortho*-alkylation was observed. Alkylation of aromatic ketones at the *ortho* position in a ruthenium(II)-catalyzed reaction has been reported by Murai and coworkers, this is an outstanding example of sp^2-CH/olefin coupling and a decisive breakthrough in efficiency and selectivity.[4] However, while the reaction shows a high efficiency for vinyl silane or vinyl siloxane, it exhibits limitations for other olefins, for example low reactivity for 1-alkenes bearing allylic protons, probably because of facile double bond isomerization, and no reactivity for internal olefins and α,ω-dienes.[5] Herein, we report an efficient *ortho*-alkylation of aromatic imines with various olefins by using Wilkinson's complex ($[Rh(PPh_3)_3Cl]$ (**3**)) and hydroacylation. This *ortho*-alkylation is chelation-assisted and shows generality as well as regioselectivity, and high efficiency.

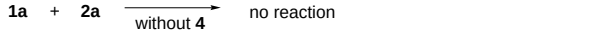
Treatment of the aldimine **1a** [Eq. (1)] with *tert*-butylethylene (**2a**) at 170 °C for 6 h with **3** (2 mol% based upon **1a**)



(1)

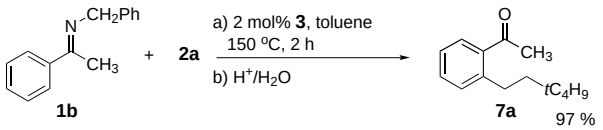
and 2-amino-3-picoline (**4**; 10 mol% based upon **1a**) as a cocatalytic system gave, after hydrolysis, compound **5a** in 90% yield along with a small amount of **6a** (5%). Compound **6a** is a hydroacylated product of **1a** and is formed by a transimination reaction, while **5a** is both a hydroacylated and an *ortho*-alkylated product. Of the various aldimines employed **1a**, prepared from benzylamine and benzaldehyde, showed the best reactivity for this simultaneous hydroacylation and *ortho*-alkylation.[3]

Compound **1a** did not react with **2a** without the cocatalyst **4** [Eq. (2)],[2] whereas, the ketimine **1b** (which is the benzylimine of acetophenone) was *ortho*-alkylated by **2a** in the



(2)

presence of **3** alone, to give **7a** in 97% yield [Eq. (3)]. These results show that the rhodium(I)-catalyzed *ortho*-alkylation takes place in ketimines, not in aldimines and that there is no *ortho*-alkylation without hydroacylation.



(3)

Ketimine **1b** was very reactive in the *ortho*-alkylation reaction with **3**; thus, various olefins were tested in reactions with this ketimine **1b** and **3** as catalyst (Table 1). In contrast to

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[**] This work was supported by the Brain Korea 21 Project, the Yonsei University Faculty Research Grant (1999), and the KOSEF (No. 97-05-01-05-01-3).

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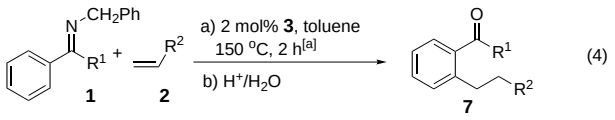
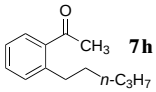
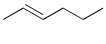
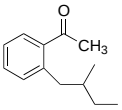
Table 1. The Rh^I-catalyzed *ortho*-alkylation of various ketimines and olefins [Eq. (4)].

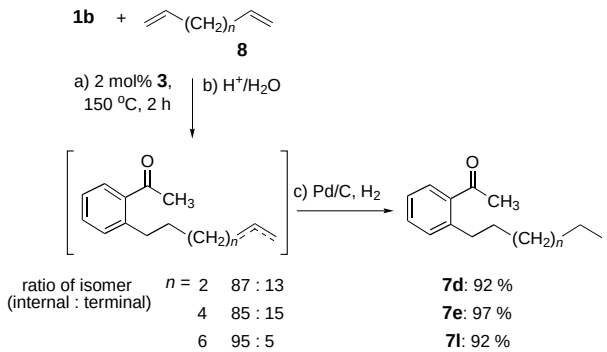


1 2 7 (4)

Entry	Ketimine R^1		Olefin R^2		Product	Yield [%][b]
1	CH_3	(**1b**)	tC_4H_9	(**2a**)	**7a**	97 (100)
2	CH_3	(**1b**)	C_6F_5	(**2b**)	**7b**	91 (100)
3	CH_3	(**1b**)	Cy	(**2c**)	**7c**	65 (68)
4	CH_3	(**1b**)	n-C_4H_9	(**2d**)	**7c**	94 (97)[c]
5	CH_3	(**1b**)	n-C_6H_{13}	(**2e**)	**7e**	71 (78)[d]
6	CH_3	(**1b**)	n-$C_{10}H_{25}$	(**2f**)	**7f**	82 (92)[d]
7	CH_3	(**1b**)	$(CH_3)_3Si$	(**2g**)	**7g**	92 (96)
8	CH_3	(**1b**)		(**2h**)	 **7h**	95 (96)
9	CH_3	(**1b**)		(**2i**)	**7d**	42 (47)[d]
10	CH_3	(**1b**)		(**2j**)	 **7i**	35[d]
11	CH_3CH_2	(**1c**)	(**2g**)		**7j**	93 (100)[e]
12	n-C_5H_{11}	(**1d**)	(**2g**)		**7k**	73 (80)[f]

[a] Reactants: **1** (0.324 mmol), **2** (0.324 mmol), **3** (0.00649 mmol), toluene (0.1 g) and molecular sieves. [b] GC yields are given in parentheses. [c] 1.62 mmol of **2d** was used. Reaction time was 6 h. [d] 0.972 mmol of **2** was used. Reaction time was 6 h. [e] Included 12% of the di-*ortho*-alkylation product. [f] Included 16% of the di-*ortho*-alkylation product.

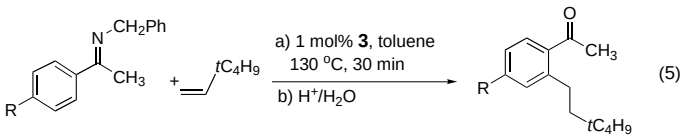
Murai's ruthenium(II)-catalyzed *ortho*-alkylation,[4, 5] with our rhodium(I) system various 1-alkenes with or without allylic protons were used successfully in the *ortho*-alkylation of ketimines (Table 1, entries 1–6). Even α,ω-dienes (**8**; Scheme 1), which did not react in Murai's system, underwent



Scheme 1. The *ortho*-alkylation of α,ω-dienes and subsequent reduction.

high-yielding *ortho*-alkylation reactions with our system. However, the *ortho*-alkylation only occurred at one end of the diene, not at both ends.[6] Remarkably, the internal olefin **2h** reacted (via isomerization to the terminal olefin 1-pentene), with **1b** to yield the linear alkylated product **7h** in high yield (Table 1, entry 8). Even sterically hindered dialkyl-substituted olefin **2j** underwent a moderately successful *ortho*-alkylation reaction (entry 10).

With *para*-substituted ketimines [Eq. (5)] electron-withdrawing substituents gave much better reactivity than electron-donating ones; this is in contrast to the *ortho*-alkylation

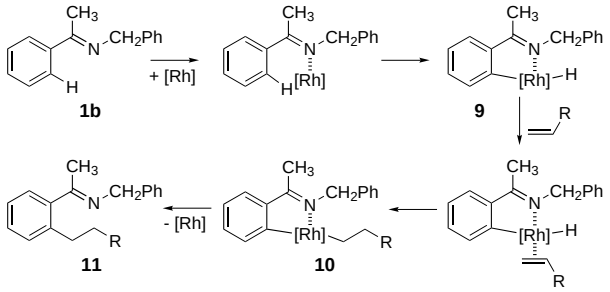


(5)

R = CF_3 (**1e**) **7m**: 76 %
H (**1b**) **7a**: 56 %
CH_3O (**1f**) **7n**: 42 %

of aromatic ketones, reported by Murai and co-workers, in which electron-withdrawing substituents retarded the reaction, whereas electron-donating ones accelerated it.[7]

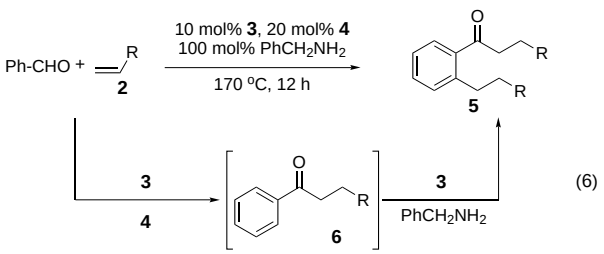
Our Rh^I-catalyzed *ortho*-alkylation is believed to occur by the mechanism shown in Scheme 2; the precoordination of the imine nitrogen atom to the Rh^I center assists in the



Scheme 2. The postulated mechanism for *ortho*-alkylation. [Rh] = $[Rh(PPh_3)_3Cl]$.

activation of an aromatic C–H bond, this in turn leads to the formation of the metallacycle **9**.[8] The C–H activation reaction proceeds by the oxidative addition of the *ortho*-C–H bond to the electron-rich $[Rh(PPh_3)_3Cl]$ unit;[9] olefin coordination and hydride insertion follow to give **10**. Finally, a reductive elimination produces the *ortho*-alkylated ketimine **11**.

In chelation-assisted hydroacylation,[2, 3] **4** was used as a chelation-assistance tool; in our Rh^I-catalyzed reaction, benzylamine could also be used as a chelation-assistance tool. The reaction shown in Equation (6) consists of chelation-



(6)

R = tC_4H_9 (**2a**) **5a**: 94 %
C_6F_5 (**2b**) **6b**: 24 % **5b**: 35 %
Cy (**2c**) **6c**: 10 % **5c**: 88 %
nC_4H_9 (**2d**) **6d**: 46 % **5d**: 54 %

assisted hydroacylation induced by **4** followed by imine-assisted *ortho*-alkylation effected by benzylamine. In this reaction benzaldehyde reacted with the olefins **2b–d**, **3**, **4**,

and benzylamine to yield a mixture of the ketones **6** and **5**.[10, 11] In the case of *tert*-butylethylene (**2a**), only **5a** was isolated (94% yield).

In conclusion, we identified a chelation-assisted, Rh^I-catalyzed *ortho*-alkylation reaction of ketimines with olefins. This type of *ortho*-alkylation shows generality as well as efficiency; the reactions of various olefins (including 1-alkenes, α,ω-dienes, and even internal olefins) with ketimines result in high yields of the corresponding *ortho*-alkylated products. In addition, successive Rh^I-catalyzed hydroacylation and *ortho*-alkylation of an aldehyde gave a product that has been alkylated at two sites.

Experimental Section

Full experimental details can be found in the Supporting Information.

A typical procedure for the preparation of **5a** [Eq. (6)]: A screw-capped pressure vial (1 mL) was charged with freshly purified benzaldehyde (0.216 mmol), 2-amino-3-picoline (**4**, 0.0432 mmol), benzylamine (0.216 mmol), $[Rh(PPh_3)_3Cl]$ (**3**, 0.0216 mmol), and *tert*-butylethylene (**2a**, 1.08 mmol), the mixture was then stirred in an oil bath at 170 °C for 12 h. Purification by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 5/2) gave pure 1-[2-(3,3-dimethyl-butyl)-phenyl]-4,4-dimethyl-pentan-1-one (**5a**) (0.203 mmol, 94% yield).

Received: April 11, 2000 [Z14976]

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[11] Without benzylamine, only hydroacylation occurred. The ketimine of 2-amino-3-picoline did not show any *ortho*-alkylation, probably because of the coordination of the Rh^I catalyst to the pyridine moiety.

Microreactors for Dynamic, High Throughput Screening of Fluid/Liquid Molecular Catalysis**

Claude de Bellefon*, Nathalie Tanchoux, Sylvain Caravieilhes, Pierre Grenouillet, and Volker Hessel

Today, high-throughput synthesis methodologies, such as combinatorial techniques, are applied to the discovery of pharmaceuticals, catalysts, and many other new materials.[1, 2] In the near future, huge libraries of ligands, and hence of homogeneous catalyst precursors, will be accessible. Recent reports have demonstrated the effectiveness of this approach for restricted libraries and in the case of catalysis in a single liquid phase.[2] High-throughput screening in one liquid phase should not represent a problem as long as the reactions are not too fast compared with micromixing rates. The microtitration-based apparatus (combinatorial chemistry (CC) factory)[2g] fulfils the requirement of ensuring reproducible tests on microquantities of samples,[2] despite uncertainties attributed to the agitation process.[2b] However, numerous reactions of interest, such as hydrogenation, carbonylation, and hydroformylation, operate in gas/liquid or gas/liquid/liquid systems.[3] Inadequate control of phase and catalyst presentation, a result from nonoptimized agitation, may dramatically affect the estimation of selectivity and reactivity. Many enantio- and regioselective-catalyzed reactions, susceptible to mass transport effects, are known.[4, 5] That may well be the explanation for the deceptively low enantiomeric excess ($ee < 20\%$) obtained in the screening of a 63-member library of rhodium/phosphane catalysts for asymmetric hydrogenation.[2a] Thus, a major challenge is to develop special reactors[1b] for rapid catalyst screening, that would ensure good mass and heat transport in a small volume.[6]

Herein we describe a new concept to achieve high-throughput screening (HTS) of polyphasic fluid reactions. Two test reactions, a liquid/liquid isomerization and a gas/liquid asymmetric hydrogenation, have been chosen to validate our approach to HTS experiments.

As a liquid/liquid test reaction, the isomerization of allylic alcohols, a process currently of industrial interest in the field of geraniol chemistry[7] was targeted [Eq. (1)].

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[**] This research was funded by the Région Rhône-Alpes, the CNRS, and the Ecole Supérieure de Chimie Physique Electronique de Lyon. S.C. is supported by a grant of the French Ministry of Education. Many thanks to Prof. D. Sinou for a gift of CBDTS.

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  0044-8249/00/11219-3584 $ 17.50+.50/0