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Rhodium-catalyzed alkylation of aromatic azines with alkenes via C–H bond activation

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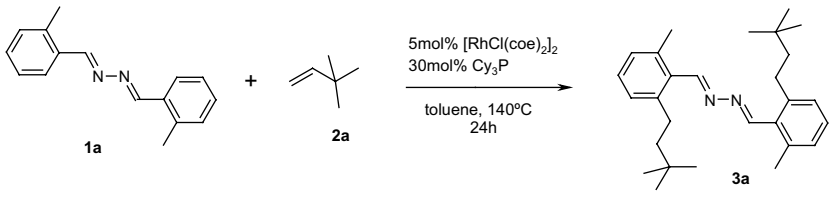
Abstract—The aromatic azines reacted with terminal alkenes under a rhodium catalyst $[RhCl(coe)_2]_2$ and Cy_3P to give the alkylated products with good to high isolated yields. The azines bearing H and *o*-CH_3, *p*-CH_3 and *p*-CH_3O groups have high reactivities, but *m*-CH_3O, *p*-Cl, *p*-F exhibit low reactivities.

Transition metal catalyzed C–C bond formations involving the C–H bond activations have recently attracted much attention.[1] By using the C–H bond activation, alkylation and alkenylation of the aromatic ring through the coupling reaction with alkenes and alkynes has been reported by us[2] and other groups.[3–11] Azines are valuable intermediates for syntheses of heterocyclic compounds[12] and especially, good candidates as nonlinear optical materials.[13] Moreover, azine derivatives have important biological properties.[14] In spite of many reports of C–C bond formation, the regioselective alkylation of aromatic azines is rare. Generally, the main reactions of aromatic azines by transition metal complexes are N–N bond cleavage of the azines and coordination of metal complexes with the azines.[15] Very recently, Imhof reported that both the N–N bond cleavage and the ethylation of naphtylazine take place in the presence of a ruthenium catalyst such as $Ru_3(CO)_{12}$ and ethylene (20 bar).[16] This report inspired us to carry out the alkylation of aromatic azines with terminal alkenes in the presence of a rhodium catalyst. We have found that aromatic azines reacted with terminal alkenes in the presence of a rhodium catalyst to give the alkylated aromatic azines in excellent yields; benzonitriles, the products resulting from N–N bond cleavage, could be detected in the trace amount in reaction mixtures by GC–MSD. The rhodium catalytic system, $[RhCl(coe)_2]_2$/Cy_3P, is well known as an excellent catalytic system for the alkylation of heteroaromatic compounds with alkenes via C–H bond activation.[2a,c,h,k,5a] First of all, we examined whether the N–N bond of aromatic azine **1a** cleavages by the rhodium catalytic system or not in the absence of alkenes. Fortunately, aromatic azine **1a** was recovered without damage in this reaction system. With these results, aromatic azine **1a** reacted with 3,3-dimethyl-1-butene **2a** (5 equiv.) in the presence of $[RhCl(coe)_2]_2$ (5 mol %) and Cy_3P (30 mol %) in toluene at 140 °C for 24 h to give the anti-Markovnikov *ortho* di-alkylated product **3a** in 89% isolated yield after chromatographic isolation (see Scheme 1). When 10 equiv of



Scheme 1.

Keywords: Alkylation; C–C bond formation; C–H activation; Rhodium catalyst; Aromatic azines.
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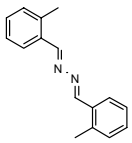
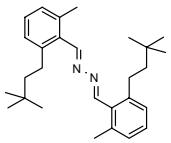
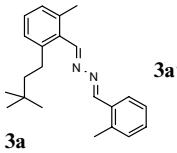
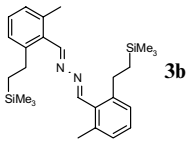
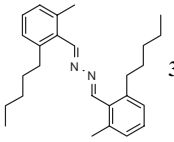
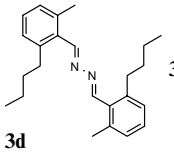
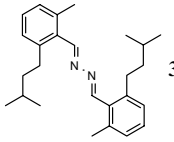
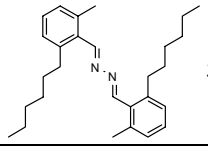
Table 1. The results of the alkylation of aromatic azines with terminal alkenes[a]

Run	Azine	Alkene (equiv)	Major product	Yield[b] (%)	Mono:di[c]
1	 **1a**	CH_2=CH_2Bu^t **2a** (5)	 **3a**	88.6	1:>99
2[d]	**1a**	**2a** (5)	 **3a′**	62	84:16
3	**1a**	**2a** (10)	**3a**	94.6	1:>99
4	**1a**	CH_2=CH_2SiMe_3 **2b** (5)	 **3b**	80.5	11:89
5	**1a**	1-Pentene **2c** (5)	 **3c**	83	33:67
6	**1a**	**2c** (10)	**3c**	99.8	9:91
7	**1a**	1-Butene **2d** (5)	 **3d**	88.8	36:64
8	**1a**	**2d** (10)	**3d**	97.9	3:97
9	**1a**	CH_2=CH_2CHMe_2 **2e** (10)	 **3e**	94.2	3:97
10	**1a**	1-Hexene **2f** (10)	 **3f**	94.5	43:57

[a] Azine: $[RhCl(coe)_2]_2$:Cy_3P = 1:0.05:0.3, toluene, 140 °C, 24 h.
[b] Isolated yields.
[c] The ratios were determined by ^1H NMR and/or GC.
[d] 10 mol % of Wilkinson's catalyst was used.

the alkene was used, an isolated yield of the product increased to 95%. In this reaction system, an increase of the equivalent of alkenes used gave high yields of the alkylated products. This result implies that excess of alkene helps the ligand dissociation to form an active catalytic species in reaction media. The results of alkylation are listed in Tables 1 and 2.

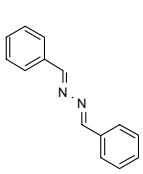
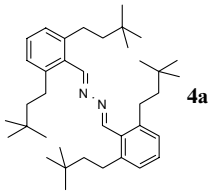
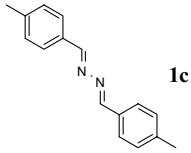
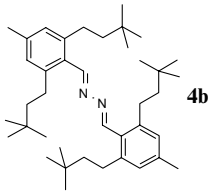
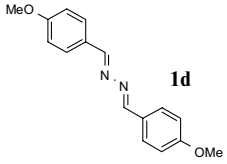
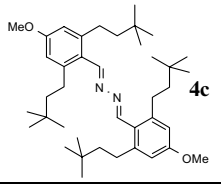
When Wilkinson's catalyst, $RhCl(PPh_3)_3$ instead of $[RhCl(coe)_2]_2/Cy_3P$, was used, this reaction gave the mono-alkylated product **3a′** as the major product (**3a**:**3a′** = 16:84, 62%) under the similar reaction conditions (Table 1, run 2). We have already reported that as the catalytic ligand, Cy_3P was found to be more effective than PPh_3.[2c] Like results reported, it implies that Cy_3P is better than PPh_3 as a phosphine ligand for the alkylation of aromatic azines. Toluene as the reaction solvent is superior to THF: in the case of the alkylation of aromatic aldimines, toluene is inferior to THF.[2k]

Other terminal alkenes such as vinyltrimethylsilane (**2b**), 1-pentene (**2c**), 1-butene (**2d**), 3-methyl-1-butene (**2e**), 1-hexene (**2f**) also worked as good partners for this alkylation (Table 1, runs 4–10).

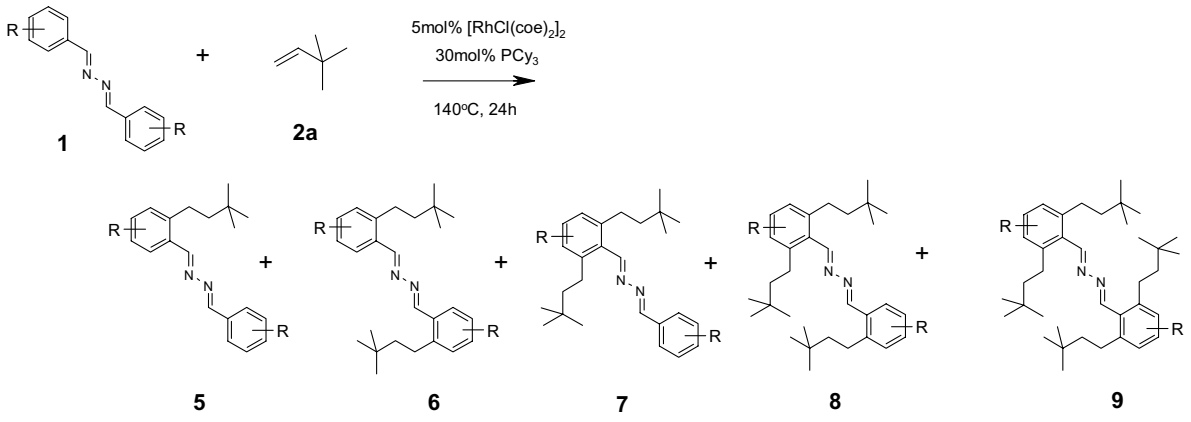
Unfortunately, alkyne such as 2-butyne and allyl ether did not work.

Neutral aromatic azine **1b** having four reaction sites gave the tetra-alkylated product in high yields along

Table 2. The results of the alkylation of aromatic azine **1b–d** with **2a**[a]

Run	Azine	Alkene	Major product	Yield[b] (%)	Mono:di:tri:tetra[c]
1	 **1b**	**2a**	 **4a**	92.2	0:0:<1:99
2	 **1c**	**2a**	 **4b**	93.3	0:0:<1:99
3	 **1d**	**2a**	 **4c**	98.2	0:0:<1:99

[a] Azine: $[RhCl(coe)_2]_2$:Cy_3P:**2a** = 1:0.05:0.3:10, toluene, 140 °C, 24 h.
[b] Isolated yields.
[c] The ratios were determined by ^1H NMR and/or GC.



1	**2a** (eq.)	Yield (%)	**5**	**6**	**7**	**8**	**9**
1e (R=*m*-OCH_3)	5	58	66	28	-	6	-
1e	10	81	34	41	5	17	3
1f (R=*p*-F)	10	87	16	7	20	13	44
1g (R=*p*-Cl)	10	93	6	4	22	18	50

Scheme 2.

with trace amounts of tri-alkylated product (Table 2, run 1). Aromatic azines **1c** and **1d** having electron donating groups such as *p*-methyl and *p*-methoxy groups also gave the tetra-alkylated products in high isolated yields (Table 2, runs 2 and 3).

Another azine **1e** having *m*-methoxy group showed a slower reaction rate than that of **1d** (see Scheme 2). It may be due to the steric hindrance to the approach of Rh metal for C–H bond activation. Azine **1e** reacted with **2a** (5 equiv) to give mono-alkylated product as a major product together with di- and tri-alkylated products. In this reaction, the alkylation takes place at less hindered reaction site. When 10 equiv. of **2a** were used, ratio of di-alkylated product increased to 41%.

Aromatic azines **1f** and **1g** having electron withdrawing groups reacted slower than azines having neutral and electron-donating groups (see Scheme 2).

From the above results, electron donating groups in the aromatic ring showed excellent reactivities, but electron withdrawing groups showed low reactivities. These results imply that an intermediate, formed after the nitrogen in the aromatic azine coordinated by rhodium metal centre, is stabilized by a contribution of the electron donation and the bonding between the nitrogen and the rhodium centre becomes stronger than that of the parent azine.

In conclusion, we have found that aromatic azines reacted with alkenes under a rhodium catalyst to give the alkylated products with good to high yields. The azines bearing H and *o*-CH_3, *p*-CH_3 and *p*-CH_3O groups have high reactivities, but *m*-CH_3O, *p*-Cl, *p*-F exhibit low reactivities.

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