Intermolecular Heck Methylations

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Catalytic Amide-Mediated Methyl Transfer from Silanes to Alkenes in Fujiwara–Moritani Oxidative Coupling**

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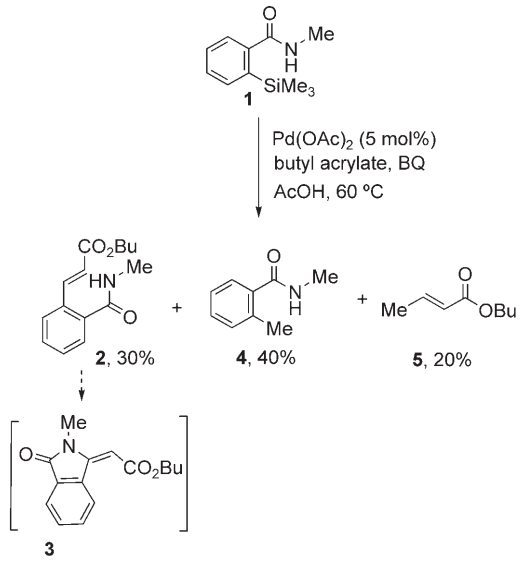
We report the discovery of a catalytic procedure for the silyl-moderated methylation of electrophilic alkenes under oxidative coupling conditions. Intermolecular alkyl transfers in Heck-type reactions have previously proved elusive.[1]

Directing groups play an important part in palladium-catalyzed aromatic C–H activation processes.[2] Most of these reactions are considered to involve a palladacycle intermediate. The electrophilic nature of the reactive Pd entity[3] indicates that C–Si displacement will be comparably feasible. This could lead to complete regiochemical control and possibly broader reactivity, given the superior leaving-group propensity of silicon over hydrogen in electrophilic aromatic substitution.[4] In practice, the desired pathway is fraught with competing side reactions. Scheme 1 offers a specific example, starting with the benzamide **1**. The expected coupling product **2** is indeed formed in modest yield, although it is slowly converted into a secondary cyclized product **3**.[5] The main product **4** is the result of ring-methylation, and a significant quantity of methyl crotonate **5** is also obtained; compound **5** is formally the product of a Heck reaction.

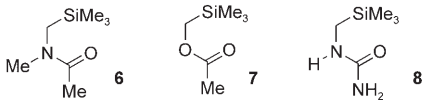


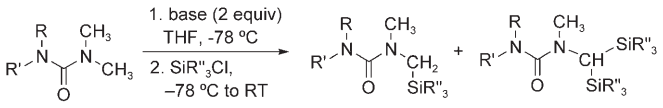
Scheme 1. The observation of by-products arising from Si–Me activation in a catalytic transformation. BQ = benzoquinone.

These latter products require cleavage of Si–Me from the trimethylsilyl group under Pd catalysis.[6] A feasible explanation follows the results of Nakao, Hiyama, and co-workers, who demonstrated that Si–aryl activation and transfer in palladium-catalyzed couplings is facilitated by a neighboring alkoxide group. The 2-alkoxymethylphenyl group coordinates to silicon, activating an axial aryl group in the ensuing five-coordinate species.[7]

These intimations of Si–Me activation in catalysis were studied under standardized conditions. The simple trimethylsilylmethyl amide **6**[8] and trimethylsilylmethyl ester **7** were employed. Ureas have comparable or superior basicity to amides[9] and have recently found use as directing groups in metal-catalyzed reactions.[10] This, together with our own observations, prompted application of compound **8** which is commercially available. Lateral lithiation of tetramethylurea, following an analogy from Clayden's work,[11] gave only 5% of the desired products **9a** and **9b**. Dimethylarylurea precursors were more successful; the major isolated product was disilylated **10b** or **11b**.[12] The same protocol was employed to prepare both bis-Ph_2MeSi derivative **12b** and its $SiEt_3$ analogue **13b**. (Scheme 2).

Overall, the alkylureas were far more reactive than other trimethylsilyl compounds in methyl transfer to butyl acrylate (Table 1). Closely related disilyl compounds **10b** and **11b** were especially effective (Table 1, entries 5 and 6) . In the presence of **10b** to the extent of 0.18 equivalents based on butyl acrylate, butyl crotonate was formed in 78% yield. This





R = R' = R" = Me	**9a**, 5%	**9b**, 5%
R = H; R' = Ph; R" = Me	**10a**, 15%	**10b**, 45%
R = H; R' = *m*-An; R" = Me	**11a**, 15%	**11b**, 25%
R = H; R' = *m*-An; $R"_3 = Ph_2Me$		**12b**, 35%
R = H; R' = Ph; R" = Et	**13a**, 5%	**13b**, 44%

Scheme 2. Trimethylsilylmethyl derivatives **6**–**8** used to screen reactivity in catalytic methyl transfer. Mono- and disilylated products **9**–**13** were separated by silica gel chromatography.

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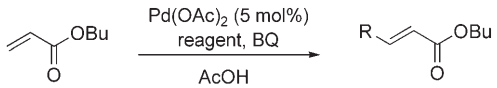
Table 1: Comparative reactivity of silylmethylureas, amide, and ester in alkyl-transfer reactions.[a]



Entry	Reagent	*t* [h]	*T* [°C]	Yield [%]
1	**6**	6	70	90[b]
2	**7**	72	80	30[b,c]
3	**8**	8	70	70[b,d]
4	**9a**	0.66	70	>90[b]
5	**10b**	0.75	70	>90[b]
6	**11b**	2	60	90[b]
7	**12b**	12	20	78[e]
8	**13b**	10	75	10[f]

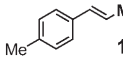
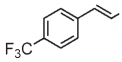
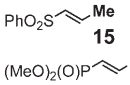
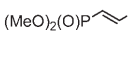
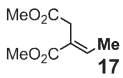
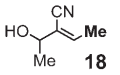
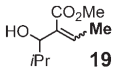
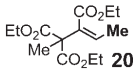
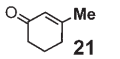
[a] 1 equiv of monosilyl reagents, 0.5 equiv of disilyl reagents (see Scheme 2). [b] R = Me. [c] Competing alkene acetoxylation. [d] Competing alkene acetoxylation and dimethylation. [e] 4:1 preference for R = Ph over R = Me. [f] R = Et; acetoxylation is the dominant reaction with minor ethylation.

demonstrates that all three silicon-bound methyl groups are available for transfer, although the second and particularly the third steps are slower than the first. In reaction of **12b**, methyl transfer competes to some extent with phenyl transfer. At present, utility is limited to methylations, since the triethylsilyl reagent **13b** is ineffective.

The scope of reaction was further explored using the readily prepared disilylurea **10b**. Styrenes reacted with this methyl-transfer agent to form **13** and **14** with high stereoselectivity at ambient temperature; at higher temperatures, greater amounts of *Z* isomer and dimethylated product were observed (Table 2, entries 1 and 2). In separate experiments, *p*-methylstyrene displays similar initial reactivity to *p*-trifluoromethylstyrene but tailed in the latter part of the reaction. When the two reactants are run together, tailing disappeared and they exhibited similar reactivity throughout. This indicates that stronger coordination of the more electrophilic alkene stabilizes the catalyst. The electron-deficient vinylsulfone and vinylphosphonate gave products **15** and **16** smoothly (Table 2, entries 3 and 4), and dimethyl itaconate reacted with high selectivity to give the *E* isomer **17** (Table 2, entry 5). The slower formation of (*Z*)-**18** from the Baylis–Hillman derived precursor reflects competing participation from the OH function, and weaker stereocontrol by CN compared to CO_2R (Table 2, entry 6). Formation of **19** by methylation of Baylis–Hillman precursor was slow at 70 °C and gave 40 % of a 58:42 (*E*/*Z*) mixture after 3 h (Table 2, entry 7). Formation of **20** was also sluggish (33 %, 1 h, 70 °C) but favors the *Z* isomer (Table 2, entry 8). In such slower reactions, benzoquinone is consumed in excess of the methylated product formed, indicating oxidative side reactions. The procedure also worked with cyclohex-2-enone (Table 2, entry 9), although some saturated product was formed concurrently.[13]

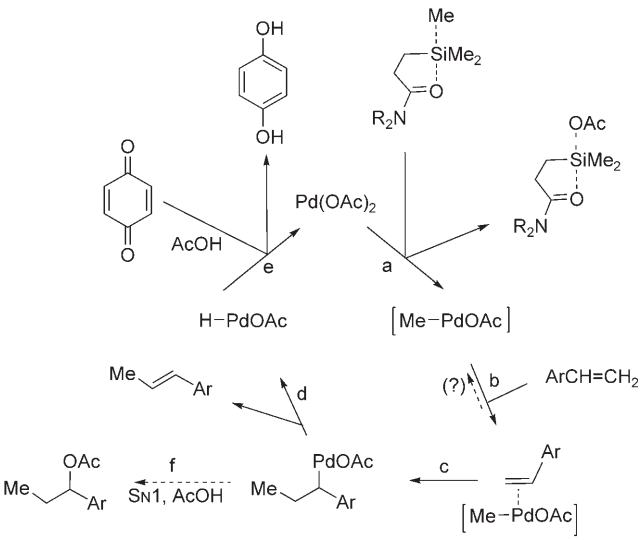
Further examples show limitations to the present methodology but help elucidate the mechanism. With *p*-methoxystyrene, **22a** and **22b** were isolated (ratio ca. 4:1), indicating solvolytic C–Pd cleavage to form the stabilized benzyl cation.

Table 2: The synthetic scope of the methyl-transfer method.[a]

Entry	*t* [h]	*T* [°C]	Product[b]	Conv. [%][c]	*E*/*Z*/Di[d]
1	1	70	 **13**	95(85)	92:4:4
	20	20		93	93:1:6
2	10	20	 **14**	99(86)	87:1:13
3	16	20	 **15**	97(80)	98:1:1
4	3	50	 **16**	94(80)	84:8:8
5	0.5	70		90	92:8:0
	30	20	**17**	95(90)	99:1:0
6[e]	8,16	40,70	 **18**	85(73)	1:99:0
7	3	70	 **19**	40	58:42:0
8	1	70	 **20**	33	1:99:0
9	2	70	 **21**	62[f]	

[a] Reactions were carried out in AcOH solution with 5 mol % $Pd(OAc)_2$, 1 equiv benzoquinone, and 0.5 equiv **10b** based on alkene. [b] Precursors to compounds **13**–**21** have H atoms at the site of the highlighted methyl groups. [c] Yields of isolated product in parentheses. [d] Di: α,α′-disubstituted product. [e] Carried out with 10 mol % catalyst and 2 equiv benzoquinone, 8 h at 40 °C then 16 h at 70 °C. [f] 3-Methylcyclohexanone is the minor product.

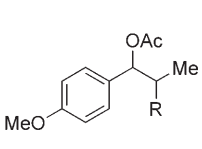
Such formation of acetates finds analogy in the original work of Fujiwara and Moritani on Pd^{II} C–H activation/coupling.[14] It may be understood in the context of a catalytic cycle (Scheme 3, step f), based on previous postulates for Heck reactions under oxidative conditions.[15]



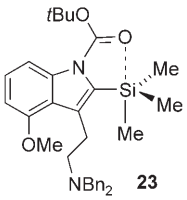
Scheme 3. Proposed pathway for Si–Me activation and transfer to alkenes: a) methyl transfer to Pd, b) alkene addition, c) alkene insertion, d) Pd–H elimination in competition with f) S_N1 solvolysis (Ar = 4-$MeOC_6H_4$), e) reoxidation to Pd^{II}.

To our knowledge, the catalytic activation of a trimethylsilyl group towards C–C coupling has not been observed previously. Stoichiometric methyl transfers from silicon to palladium, and some inefficient catalytic reactions therefrom, were recorded earlier.[16] Hiyama and Hatanaka have demonstrated effective Pd-catalyzed aryl–methyl coupling with the hypervalent reagent $Me_3SiF_2^-$.[17]

We propose that Si–Me activation is caused by direct donor bonding between the amidic oxygen and silicon atoms (step a of Scheme 3) which is supported by structural investigations of Bassindale and co-workers.[18] In amides and related substrates with a capacity for intramolecular O–Si association, an electronegative group on silicon is labilized. The effect ranges from modest changes in bond lengths (Si–F) to ion-pair dissociation (Si–OTf). In principle, the same mechanism could labilize the Si–Me bond. The CDS database indicates 26 structures for which intramolecular amide O–Si interaction through a five-ring chelate are conceivable.[19] For just two of these (**23** and **24**), an O–Si distance of < 3.0 Å indicates association, the diametric Si–Me bond is lengthened, and the remaining substituents at the silicon center move towards planarity. This was previously unrecognized and provides support for the proposed activation step a in Scheme 3 .



22a, R = H
22b, R = Me



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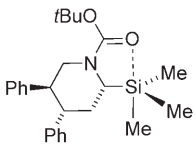

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Further work is in progress to extend the scope and enhance the catalytic reactivity of alkyl transfer.

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