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Organic Synthesis in Ionic Liquids: The Stille Coupling

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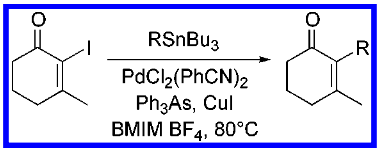
ABSTRACT



The Stille coupling reaction has been performed in 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM BF$_4$), a room-temperature ionic liquid (RTIL). Use of this solvent system allows for facile recycling of the solvent and catalyst system, which can be used at least five times with little loss in activity. An interesting preference in starting catalyst oxidation state for use with aryl bromides and aryl iodides was observed.

Transition-metal catalyzed cross-coupling reactions are versatile and highly useful transformations leading to a wide variety of compounds.[1] Of the variety of reactions that fall into this category, the Stille reaction has been one of the most heavily used in the preparation of a wide variety of materials including polyenes, diaryls, and aromatic carbonyl compounds.[2] Part of this utility stems from the fact that the organometallic coupling partner, an organostannane, is air and moisture stable and thus readily prepared and stored. Further, the coupling conditions are compatible with a wide array of functional groups. Indeed, the one major limitation to this particular transformation is the toxicity of the organotin reagents and byproducts.

There is another problem that is encountered in not only the Stille coupling but really in all transition-metal catalyzed cross-coupling reactions: the catalyst itself. Most of these transformations are catalyzed by palladium species, which is an expensive metal. Further, the desired reactivity can often only be achieved by using expensive and/or toxic ligands.[3] Ideally, one would like to be able to recover and recycle the entire catalyst system but avoid the challenges presented by either mounting the catalyst on a solid support or by preparing designer ligands for use in aqueous or fluorous biphasic systems.[4]

Recently, a new alternative solution for catalyst recycling has been reported. This involves the use of room-temperature ionic liquids (RTILs), in essence salts that are liquid at or below room temperature.[5] These solvents have found application in a wide variety of organic transformations, particularly transition-metal catalyzed transformations.[6] A large part of the interest in these solvents is due to the ease

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[1] For a recent review, see: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, CA, 1999.

[2] For a review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

[3] For example, coupling reactions of aryl chlorides generally fail to afford any of the desired product. However, the biphenylphosphine ligands reported by Buchwald have extended the scope of Suzuki and siloxane couplings to encompass aryl chlorides as well as hindered aryl bromides. For examples, see: Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137.

[4] For a recent volume discussing alternate solvents and reagent recycling, see: *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Topics in Current Chemistry, Vol. 206; Springer-Verlag: Berlin, 1999.

[5] For a recent review, see: Welton, T.; *Chem. Rev.* **2000**, *100*, 2071−2083.

[6] For examples utilizing this approach not included in ref 5, see the following. Asymmetric epoxidation: Song, C. E.; Rho, E. J. *Chem. Commun.* **2000**, 837−838. Heck reaction: Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur, J*, **2000**, *6*, 1017−1025. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997. Friedel−Crafts alkylation: Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *Chem. Commun.* **2000**, 1695. Oxidation of aldehydes: Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627. Hydrogenations: Steines, S.; Wasserscheid, P.; Driessen-Hoelscher, B. *J. Prakt. Chem.* **2000**, *342*, 348. Suzuki reaction: Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249. Aza-Diels−Alder reaction: Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, 137. Trost-Tsuji Reaction: Toma, S.; Gotov, B.; Kmentova, I.; Solcaniova, E. *Green Chem.* **2000**, 149.

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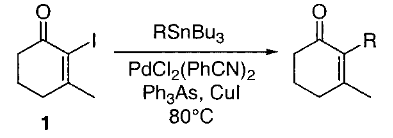
with which the reaction products can be removed from the solvent and catalyst by either distillation or extraction with a nonpolar organic solvent such as hexane, benzene, or diethyl ether. The remaining RTIL solution retains the catalyst and can be reused multiple times with little to no loss of activity.[7]

In the context of another research effort in our labs, we were interested in applying these RTIL conditions to the Stille coupling. In particular, we were focusing on the coupling of α-iodoenones such as **1** (Table 1). This type of coupling was reported earlier by Johnson and co-workers.[8] After extensive screening, they determined that the combination of *N*-methylpyrrolidinone (NMP) with a catalyst composed of bis(benzonitrile)palladium(II) chloride, triphenylarsine, and copper(I) iodide afforded the desired Stille products in good to excellent yields. Given the reported polarity of RTILs[9] and the obvious desire to recycle this multicomponent catalyst system, we chose this to be our starting point for the investigation of the Stille coupling in RTILs.

Table 1. Stille Coupling of α-Iodoenones[a]



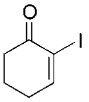
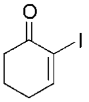
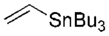
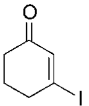
entry	solvent	R	time	yield[b]
1	NMP	vinyl	30 min	95%[c]
2	NMP	*p*-Tolyl	7 h[d]	89%[c]
3	BMIM BF_4	vinyl	2 h	82%
4	BMIM BF_4	vinyl	2 h	78%[e]
5	BMIM BF_4	vinyl	2 h	72%[f]
6	BMIM BF_4	phenyl	8 h	83%
7	BMIM BF_4	phenyl	8 h	90%[e]
8	BMIM BF_4	phenyl	8 h	92%[g]

[a] All reactions performed using 5 mol % of palladium catalyst. [b] Isolated yields. [c] Data from ref 8. [d] Reaction run at 110 °C. [e] Second run using recycled catalyst/media. [f] Third run using recycled catalyst/media after 24 days. [g] Third run using recycled catalyst/media.

Our choice of solvent was the readily prepared 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM BF_4) RTIL.[10] Using this solvent for the reaction of α-iodoenone **1** and vinyltributyltin afforded results comparable to those obtained using NMP as the solvent (Table 1, entries 1 and 3). Further, extraction of the product with diethyl ether afforded an ionic liquid layer that could be recycled several times with only a slight loss in activity (entries 3−5). Additionally, this ionic liquid layer could be stored for several weeks with no special precautions to exclude air or moisture and still afford comparable results to the fresh ionic liquid/catalyst system (entry 5).

Even better results were obtained in the coupling of α-iodoenone **1** with phenyltributyltin (Table 1, entries 2 and 6). In this case, product recovery actually increased slightly over three recyclings (entries 6−8). Using these same conditions, both α- and *β*-iodocyclohexenones also afforded the Stille coupling products in generally good yield (Table 2).[11]

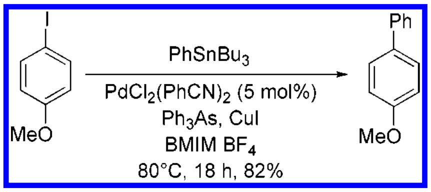
Table 2. Stille Couplings of α- and *β*-Iodoenones[a]

entry	iodide	stannane	yield[b]
1		Bu_3SnPh	66%
2			46%
3		Bu_3SnPh	86%

[a] All reactions performed using 5 mol % of $PdCl_2(PhCN)_2$, Ph_3As, and CuI. [b] Isolated yields.

Another major use of Stille couplings is in the preparation of diaryl compounds. Using the same multicomponent catalyst system used with the α-iodoenones afforded the coupling product of *p*-iodoanisole and phenyltributyltin in a good 82% yield (Scheme 1). Interestingly, a variety of other

Scheme 1. Coupling of Aryl Iodide



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(7) This concept was introduced by Chauvin and co-workers and emulated in many of the studies cited in refs 5 and 6. For this initial communication, see: Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *34*, 2698.

(8) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919−922.

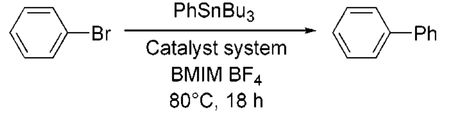
(9) There are conflicting reports regarding the polarity of ionic liquids. While at first glance these salts would appear to be highly polar, pyrene fluorescence spectroscopy indicated a dielectric constant of < 10 (Bonhote, P.; Dias, A.-P.; Papageorgiou, P.; Kalyanasundaram, K.; Graetzel, M. *Inorg. Chem.* **1996**, *35*, 1168). However, use of Reichardt's indicator dyes indicated that the polarity was similar to that of 1-propanol (Visser, A. E.; Swarloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. Proceedings of the 4th Annual Green Chemistry and Engineering Conference, Washington, DC, June 27−29, 2000; p 50). Our Stille coupling results are in keeping with BMIM BF_4 acting as a more polar solvent.

(10) The preparation of this ionic liquid is a modification of the procedure reported by Rogers and co-workers for the preparation of the PF_6 derivative (Huddleston, J. G.; Willauer, H. D.; Swarloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun.* **1998**, 1765). Details may be found in the Supporting Information.

palladium catalyst systems [$Pd(Ph_3P)_4$, 30%; $Pd(OAc)_2$/$P(o\text{-Tol})_3$, 0%; $Pd_2(dba)_3$/$P(t\text{-Bu})_3$, <5%] afforded little if any of the desired coupling product.

A rather different trend was noted in the coupling of aryl bromides. Application of the conditions that worked well for the aryl iodides to the coupling of bromobenzene with phenyltributyltin afforded biphenyl in only 35% yield (Table 3, entry 1). However, using a palladium(0) catalyst source such as $Pd(Ph_3P)_4$ afforded the desired product in 90% yield (entry 2). Rather impressively, this ionic liquid solution could be recycled, following product extraction with diethyl ether, to afford equally high yields of biphenyl (entry 3).[12]

Table 3. Coupling of Aryl Bromides[a]

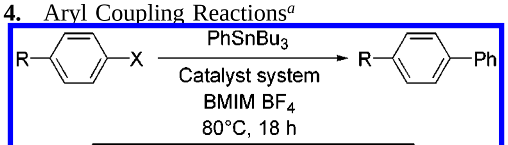


entry	catalyst system	yield[b]
1	$PdCl_2(PhCN)_2$, Ph_3As, CuI	35%
2	$Pd(Ph_3P)_4$	90%
3	$Pd(Ph_3P)_4$	93%[c]

[a] All reactions performed using 5 mol % of palladium catalyst. [b] Isolated yields. [c] Second run using recycled catalyst/media.

These two catalyst combinations proved to be effective for the coupling of a variety of aryl iodides and bromides as shown in Table 4. The iodides afforded good to excellent yields, even for electron-rich aromatic systems, using the multicomponent palladium(II) catalyst system, while the bromides afforded good yields for electron-deficient and moderately electron rich aromatic systems using $Pd(Ph_3P)_4$. The more electron rich *p*-bromoanisole afforded only a 15% yield of the desired Stille coupling product, which is typical for these types of couplings in conventional solvents.

Table 4. Aryl Coupling Reactions[a]

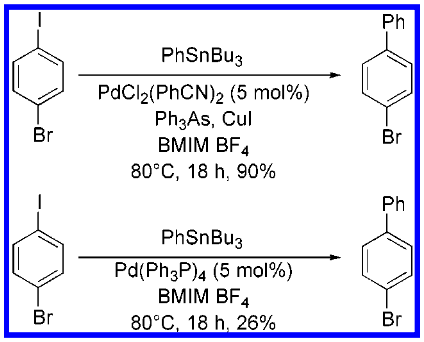


entry	R	X	yield[b]
1	H	I	80%
2	Me	I	95%
3	OMe	I	82%
4	H	Br	90%
5	Ac	Br	92%
6	Ac	Br	93%[c]
7	Me	Br	86%
8	OMe	Br	15%

[a] All reactions performed using 5 mol % of catalyst. X = Br, catalyst = $Pd(Ph_3P)_4$; X = I, catalyst = $PdCl_2(PhCN)_2$, Ph_3As, CuI. [b] Isolated yields. [c] Second run using recycled catalyst/media.

In light of this interesting selectivity that we were observing between the aryl iodides and bromides, we chose to investigate the potential for chemoselectivity by using *p*-iodobromobenzene (Scheme 2). With the palladium(II) catalyst system, we observed clean coupling with the iodide to afford 4-bromobiphenyl in 90% isolated yield.

Scheme 2. Competition Experiments



With $Pd(Ph_3P)_4$, we did not observe any coupling with the bromide, but instead isolated only a modest 26% yield of 4-bromobiphenyl. Thus, the catalyst-dependent difference in reactivity observed in the bromo and iodo series is not sufficient to overcome the inherent selectivity (I > Br) normally observed in the Stille coupling reaction. Nevertheless, catalyst choice still has a dramatic effect in the efficiency of the reaction.

Since the initial goal of this research effort was to develop a highly recyclable solvent/catalyst system, we further investigated the number of times that we could reuse both the palladium(II) and palladium(0) systems. As shown in Scheme 3, both systems can be recycled at least five times with essentially no loss in activity in the palladium(II) system and only a modest decrease in activity in the palladium(0) system. Whether this loss in activity is due to precipation of the palladium(0) from the reaction solvent or due to partial extraction of the very nonpolar catalyst during the separation phase is currently under investigation.

In summary, we have demonstrated that Stille coupling reactions can be successfully conducted in RTILs. This procedure permits extensive recycling of the solvent and catalyst without significant loss in activity. Further, an interesting catalyst selectivity for aryl bromides and aryl iodides was noted. Further investigations concerning the

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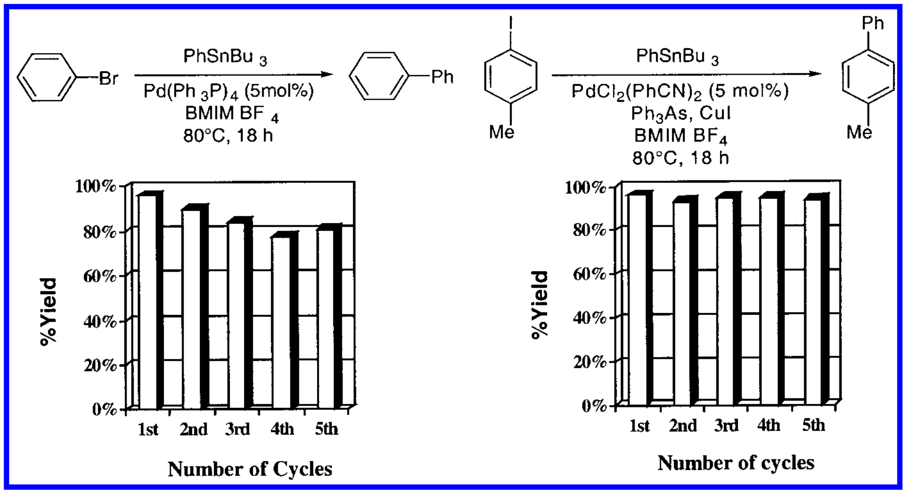
(11) **Representative procedure:** To a dry round-bottomed flask under nitrogen were sequentially added 235.9 mg (1.00 mmol) of 2-iodo-3-methyl-2-cyclohexen-1-one, 19.0 mg (0.100 mmol) of copper(I) iodide, 31.0 mg (0.100 mmol) of triphenylarsine, and 19.0 mg (0.0500 mmol) of bis(benzonitrile)palladium(II) chloride. This mixture was dissolved in 1 mL of BMIM BF_4 and was immediately lowered into an oil bath maintained at 80 °C. To this solution was added 0.35 mL (1.200 mmol) of tributylvinyltin. After stirring for 2 h, the reaction mixture was extracted with diethyl ether (10 × 10 mL). The combined organic layers were washed with saturated aqueous potassium fluoride (3 × 30 mL) The aqueous layers were combined and back-extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting oily residue was purified by flash column chromatography (5:95, then 1:9 EtOAc/Hexanes as eluent) to afford 90.3 mg (82%) of 3-methyl-2-vinylcyclohexenone as a pale yellow oil.

(12) All compounds exhibited spectral data consistent with that reported in the literature.

Scheme 3. Recycling Studies



mechanistic reasons for this phenomenon and application of these RTIL recycling conditions to other types of transition-metal catalyzed transformations are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of BMIM BF_4 and the Stille coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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