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Addition of Benzylzinc Halides to Alkenyl(phenyl)iodonium Triflates: Stereoselective Synthesis of Trisubstituted Alkenes

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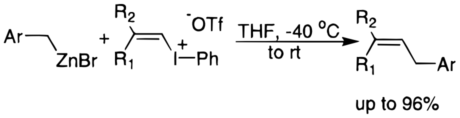
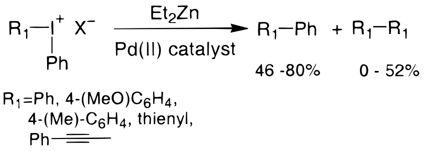
ABSTRACT



Benzylic organozinc reagents generated by insertion of zinc metal into benzyl–bromine bonds react with alkenyl(phenyl)iodonium triflates to provide single stereoisomers of trisubstituted olefins. The extremely high reactivity of the phenyliodonio moiety allows these reactions to be performed in the absence of copper salts or palladium catalysts. The reaction is performed from –40 °C to room temperature in THF. Excellent yields of the desired cross-coupled products have been obtained despite the occurrence of a competing electron-transfer-induced fragmentation.

Alkenyl(aryl)iodonium salts[3] are extremely reactive compounds and act as vinyl electrophiles with a variety of soft nucleophiles such as stable enolates, organocuprates, sulfinates, cyanides, thiolates, azides, and halides.[3,4] Iodonium salts also participate in a number of palladium-mediated couplings analogous to the Stille,[5] Heck,[6] and Suzuki[7] reactions. Conversely, organozinc halides generally only react with highly reactive electrophiles such as allylic halides and acid chlorides.[8,9] Reactions with other, less-reactive electrophiles usually require transmetalation with palladium,[10] copper,[11] or other metals to increase the reactivity and facilitate substitutions or coupling. To our knowledge, the only report of a reaction involving organozinc reagents and iodonium salts resulted in reductive coupling under palladium-catalyzed conditions (eq 1).[12] However, this reaction was performed using the more reactive diethyl zinc reagent rather than organozinc halides. Despite this discouraging report, we envisioned that the low reactivity of the organozinc



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[3] For recent reviews of hypervalent iodine compounds, see: (a) Moriarty, R. M.; Prakash, O. In *Advances in Heterocyclic Chemistry*; Katritsky, A. R., Ed.; Academic: New York, 1998; pp 1−87. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179−1255. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **1996**, *96*, 1123−1178. (d) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: New York, 1997.

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[8] Two recent monographs have appeared regarding the utilization of zinc reagents: (a) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford: New York, 1999. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: New York, 1996.

[9] For a somewhat dated but comprehensive review of Knochel's zinc chemistry, see: Knochel, P. Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

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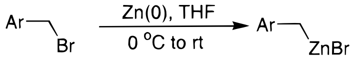
halide reagents and the extreme lability of the alkenyl(aryl)iodonium triflates would result in an efficient protocol. Further, the greatest benefit of zinc reagents is that these can be formed from organohalides even if the substrates contain functional groups such as ketones, nitriles, esters, amides, amines, sulfides, silanes, and sulfones. This is a direct manifestation of the highly covalent (and generally poorly reactive) nature of the carbon−zinc bond and is in direct contrast to typical organocuprates, Grignards and lithium reagents. We report herein our initial results of reactions between organozinc halides and alkenyl(phenyl)iodonium triflates in THF.

We examined the formation of organozinc halides by several methods including transmetalation with lithium[13] and Grignard[14] reagents as well as direct halide insertion of zinc dust. We chose benzylic bromides as initial substrates in order to provide products which would be of sufficient molecular weight to facilitate isolation on a small scale. Further, several benzylic organozinc reagents are formed easily and conveniently at or near ambient temperature.[15]

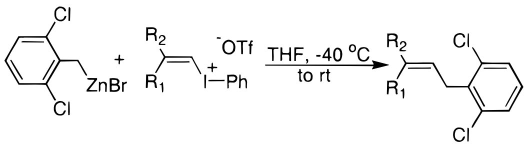
After experimenting extensively with the conditions to form organozinc halides, we found that the use of zinc foil, as initially reported by Gaudemar in 1962,[16] provided the best results. Following Knochel's procedure,[17] we activated the foil (0.25 mm; Aldrich) by addition of 1,2-dibromoethane followed by heating to reflux several times in THF. After cooling to 0 °C, a 0.5−1.0 M solution of benzylic bromide was added dropwise via addition funnel (eq 2). After TLC



(2)

1: Ar = 2,6-(Cl)$_2$-C$_6$H$_3$
2: Ar = 3-(CN)-C$_6$H$_4$
3: Ar = 2,6-(Cl)$_2$-C$_6$H$_3$
4: Ar = 3-(CN)-C$_6$H$_4$

indicated consumption of starting benzyl bromide, the reagent was added to precooled (−40 °C) THF solutions containing the appropriate recrystallized alkenyl(phenyl)iodonium salt (eqs 3 and 4). The zinc reagent solutions utilized in this study varied from 0.52 to 1.26 M. A representative example of organozinc formation is provided in the Supporting Information.



(3)

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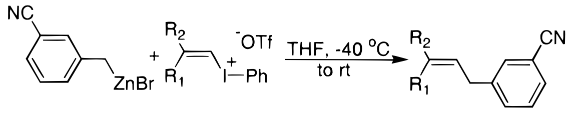
5a: R$_1$ = Et, R$_2$ = Ph
5b: R$_1$ = Et, R$_2$ = Me
5c: R$_1$ = R$_2$ = Me

6a: R$_1$ = Et, R$_2$ = Ph
6b: R$_1$ = Et, R$_2$ = Me
6c: R$_1$ = R$_2$ = Me



(4)

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5c: R$_1$ = R$_2$ = Me

7c: R$_1$ = R$_2$ = Me

After addition, the reaction temperatures were allowed to rise to room temperature and then the solutions were stirred overnight (ca. 12 h). The reactions were quenched with saturated NH$_4$Cl (1 × 2 mL), and the reaction mixtures were extracted with 1:1 hexanes/ethyl acetate (typically 4 × 2 mL), dried (MgSO$_4$), and concentrated in vacuo. Purification was performed by flash silica gel chromatography or radial chromatography using hexanes (compounds **6a**−**6c**) or 95/5 hexanes/ethyl acetate (compound **7c**). Isolated yields of purified products are reported in Table 1.[18]

Table 1. Products of Reaction between Benzylic Organozinc Halides and Alkenyl(phenyl)Iodonium Triflates

Product	Zn	additive	yields[a](%)
6a	foil	–	59, 83,[b] 95[c]
		Pd[d]	47[e]
		TEMPO	73, 85,[b] 93[c]
		CuCN•2LiCl	96,[b] 91[c]
6b	foil	–	48
		Pd[d]	42[f]
		TEMPO	57
		CuCN•2LiCl	46
6c	dust	–	48, 50
7c	foil	–	74

[a] Isolated Yields of chromatographed materials; [b] exposed to ambient laboratory light; [c] wrapped in aluminum foil to shield from laboratory light; [d] 5 mol% Bn(Cl)Pd(PPh$_3$)$_2$ was used as a potential catalyst. [e] As an inseparable mixture of product and Wurtz coupling byproduct in a 2.9/1 mixture; [f] As a 4/1 mixture of product and Wurtz byproduct.

We investigated the use of several additives during our studies. Organocuprates are documented to react with vinyl iodonium salts with high efficiency.[4] We transmetallated the zinc reagents with THF-soluble CuCN·2LiCl[17] and found that this led to somewhat ambiguous results. Although ultimately leading to our highest isolated yield (96%) of **6a**, the results were not always consistent and our highest yield of **6a** without addition of copper(I) was 95%. Because of a competing electron-transfer reaction (vide infra), we also

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(10) Transmetalations with palladium are generally catalytic in palladium. Negishi's development of the reaction bearing his name is ample evidence for its utility: Negishi, E.; Liu, F. In *Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1997; Chapter 1, pp 1−49. Stevenson, T. M.; Prasad, B.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375−8378. Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348.

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(12) Kang, S.-K.; Hong, R.-K.; Kim, T.-H.; Pyun, S.-J. *Synth. Commun.* **1997**, *27*, 2351−2356.

(13) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983−3985. Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823.

(14) Negishi, E.; Takahashi, T.; King, A. O. *Organic Synthethes*; Wiley: New York; Collect. Vol. VIII, pp 430−434.

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(16) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974.

(17) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392.

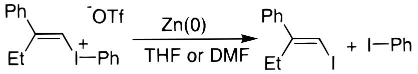
(18) Products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and were homogeneous by TLC. Compounds **6a** and **6c** also gave correct combustion analyses. Spectra and experimental details are contained in the Supporting Information.

investigated the use of TEMPO (1.0 equiv, based on iodonium salt) as a radical scavenger. As with copper(I), the presence of TEMPO did not result in a consistent improvement in product yield. We also briefly investigated the use 5 mol % of $Pd(PPh_3)_4$ and $BnPd(PPh_3)_2Cl$ as catalysts. Again, no significant improvement was observed. Finally, we evaluated *hν* as a potential radical initiator by conducting the reactions in vessels covered in aluminum foil. This appeared to provide significant benefits as **6a** was isolated in 95% yield in the absence of light and 83% yield when the reaction was exposed to ambient light using the same batches of both **3** and **5a**.

The stereochemistry shown in **6a** and **6b** has not been firmly established. In the cases of both **6a** and **6b**, only a single stereoisomeric product was observed by ^{1}H NMR spectroscopy in crude reaction mixtures. The isomers shown are based on previous results reported by Ochiai and coworkers which investigated the use of Gilman reagents with alkenyl(phenyl)iodonium tetrafluoroborates.[4] The mechanism that they proposed involves initial coordination of the cuprate to the cationic iodine atom followed by two successive reductive elimination sequences. This ultimately leads to net retention of the vinyl geometry which is present in the starting iodonium salts.[19]

To clearly define the stereochemistry of the coupled products, NOE measurements will be necessary, and firmly establishing the stereoselectivity of the reaction will require the use of stereoisomeric pairs of salts in the coupling process to observe if the opposite isomer is produced.

Although 96% was the highest yield obtained in the reaction between **3** and **5a**, we have often encountered fragmentation reactions upon performing this coupling. We believe that these are initiated by dissolved Zn(0) which donates an electron into the iodonium salt and induces the cleavage to vinyl iodide and iodobenzene. To test this assumption, we dissolved the iodonium salt in THF and DMF at various temperatures. Upon addition of freshly opened zinc dust, TLC indicated immediate formation of vinyl iodide and iodobenzene at temperatures as low as −78 °C (eq 5). The



(5)

efficacious generation of the organozinc halide reagent appears to be crucial to suppress this process. Qualitatively we have observed that an increase in Wurtz coupling product is directly correlated with an increase in the amount of fragmentation that occurs. This may be an indication of an electron-transfer process occurring which results in dissolved Zn(0) during the Wurtz coupling process.

In conclusion, we have developed a cross-coupling reaction between organozinc halides and alkenyl(phenyl)iodonium triflates which occurs under mild conditions and affords stereoisomerically pure trisubstituted alkenes. Unlike reactions of organozinc compounds with many electrophiles, the reaction described herein does not require transmetalation of the organozinc reagent in order for coupling to occur. We are in the process of developing protocols which will decrease the occurrence of electron-transfer processes which compete with coupling.

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Supporting Information Available: Spectra of compounds **6a**−**6c** and **7c** as well as detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] The stereochemistry of β,β-disubstituted alkenyl(phenyl)iodonium triflates has been verified via ^{1}H NMR spectroscopy. Hinkle, R. J.; Stang, P. J. *Synthesis* **1994**, 393−396.