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Novel Kumada Coupling Reaction to Access Cyclic (2-Azaallyl)stannanes. Cycloadditions of Cyclic Nonstabilized 2-Azaallyllithium Species Derived from Cyclic (2-Azaallyl)stannanes

Douglas M. Mans and William H. Pearson*,†

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

wpearson@berryassoc.com

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A Kumada cross-coupling reaction involving organomagnesium reagents and (3-methylthio-2-azaallyl)stannanes with a Ni(0) catalyst provided cyclic nonstabilized (2-azaallyl)stannanes in moderate to good yields. Primary alkyl, aryl, and allylic organomagnesium reagents can be used as the cross-coupling partner. In general, $NiCl_2$dppp in toluene at room temperature provided the shortest reaction times and most consistent yields. The azomethine ylides and 2-azaallyllithium species derived from these stannanes were shown to undergo efficient [3 + 2] cycloaddition reactions to provide azabicyclo[*n*.2.1]alkanes as the *endo* cycloadducts. These cycloadducts were found to be useful as starting materials for further elaboration into aza-bridged bicyclic natural and unnatural products of biological interest. Although cyclic 2-azaallyllithium species have been generated previously, this work reports the first generation and cycloaddition of entirely nonstabilized 2-azaallyllithium species. In addition a novel extension of the Kumada coupling was developed to allow for the preparation of the cyclic (2-azaallyl)stannanes, which are precursors to the nonstabilized 2-azaallyllithium species.

Introduction

The generation of highly substituted pyrrolidines via cycloaddition reactions with acyclic nonstabilized 2-azaallyllithium species, produced from the corresponding (2-azaallyl)stannanes, has proven to be useful.[1] The (2-azaallyl)stannanes are readily prepared by the condensation of the desired aldehydes or ketones with α-aminostannanes.[2] Work done in our laboratories has shown that (2-azaallyl)stannanes are excellent latent 2-azaallyllithium sources upon a tin−lithium exchange. These reactive 2-azaallyllithium species have been used in numerous total syntheses of pyrrolidine-containing natural products.[1a,3,4]

Attempts to extend the scope of this methodology to include cyclic nonstabilized (2-azaallyl)stannanes have met with limited success. Previous reports have disclosed the synthesis of the heteroatom-substituted cyclic (2-azaallyl)stannanes **2a** and **2b** and their use as cycloaddition precursors (Scheme 1).[1b,5] Whereas the cyclic (3-methoxy-2-azaallyl)stannane **2a** and the (3-methylthio-2-azaallyl)stannane **2b** could be made, all attempts to synthesize an amidine version met with failure. In addition, only the (3-methoxy-2-azaallyl)stannane **2a** was found to undergo cycloaddition reactions with alkenes. The (3-methylthio-2-azaallyl)stannane **2b** instead gave only decomposition under the cycloaddition reaction conditions.[1b] Another unforeseen obstacle was the fact that the cycloadduct **3** arising from a 3-methoxy-2-azaallyllithium invariably possessed a bridgehead methoxy group, which proved resistant to removal or conversion to another functional group under numerous conditions.[1b] Thus it was not possible to generate simple alkyl-substituted cycloadducts **4**. A possible solution to this problem would be to synthesize the unsubstituted cyclic nonstabilized (2-azaallyl)stannanes, which upon conversion to the cyclic nonstabilized 2-azaallyllithiums should participate in [3 + 2] cycloadditions to give the simple alkyl-substituted cycloadducts **4** directly.

We now report the synthesis of cyclic nonstabilized (2-azaallyl)stannanes from the corresponding cyclic (3-methylthio-2-azaallyl)stannane **2b** via a Kumada coupling of organomagnesium reagents using a Ni(0) catalyst. In addition, the generation of the corresponding cyclic 2-azaallyllithium and azomethine ylide species and their

† Current address: Berry and Associates, Inc., 2434 Bishop Circle East, Dexter, MI 48103.

(1) Leading references: (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903−921. (b) Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* **1998**, *63*, 9812−9827.

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(5) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641−2644.

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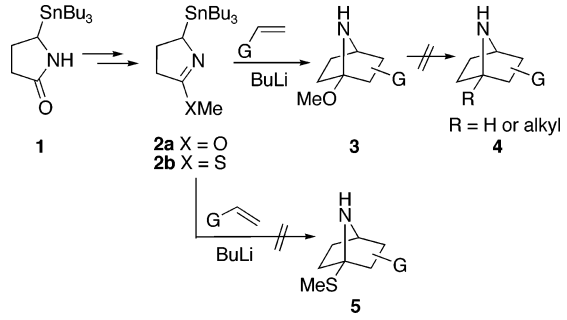
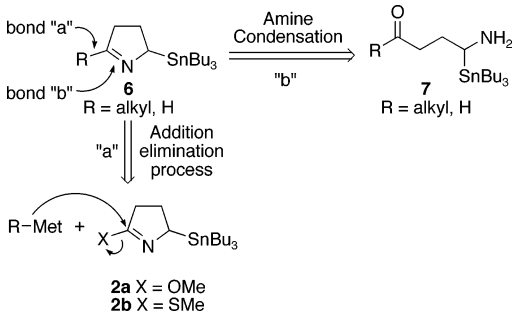
SCHEME 1. Previous Work with Heteroatom-Substituted Cyclic (2-Azaallyl)stannanes[1b]



SCHEME 2. Possible Bond Disconnections



cycloaddition with alkenes gave azabicyclo[*n*.2.1]alkanes in good yields with high *endo* selectivity.

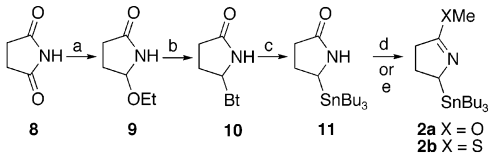
Results and Discussion

On the basis of previous work done in our laboratories,[1b,2b] two possible routes to the cyclic nonstabilized (2-azaallyl)stannanes **6** were envisioned (Scheme 2). Formation of bond a might arise from reaction of an organometallic reagent with either the methylimidate **2a** or methylthioimidate **2b** by an addition−elimination process. Alternatively, bond b may arise from an intramolecular condensation reaction of an amino ketone such as **7**. Formation of bond b was deemed less suitable because of difficulties encountered in preparing the condensation precursors. Therefore formation of bond a was pursued.

As described previously,[1b] partial reduction of succinimide **8** and in situ conversion to the known ethoxy *N*,*O*-acetal **9** was performed using the conditions reported by Speckamp (Scheme 3).[6] Conversion of **9** to the benzotriazole **10** followed by displacement with (tributyl)tinlithium[1b,7] gave the stannyl lactam **11**. Methylation with dimethyl sulfate provided (3-methoxy-2-azaallyl)stannane **2a**. Additionally, treatment of **11** with Lawesson's reagent and methylation with dimethyl sulfate generated (3-methylthio-2-azaallyl)stannane **2b**.

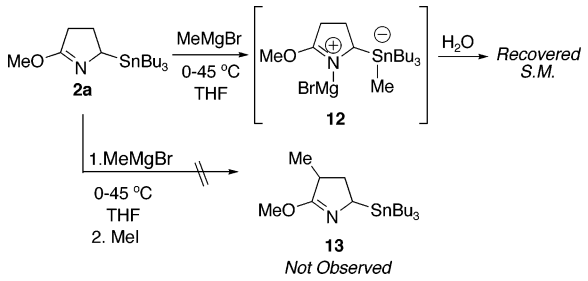
With tin precursors **2a** and **2b** in hand, the addition−elimination reaction was examined. Unfortunately, treatment of **2a** and **2b** with organomagnesium reagents under a variety of conditions failed to produce the desired stannanes **6**. Starting material was returned in all cases,

SCHEME 3. Synthesis of (2-Azaallyl)stannanes 2a and 2b[a]



[a] Conditions: (a) $NaBH_4$, 2% aq HCl, EtOH; (b) benzotriazole, AcOH, (79% from **8**); (c) Bu_3SnH, LDA, THF, 0 °C (90%); (d) Me_2SO_4, (71%); (e) (i) Lawesson's reagent, (60%), (ii) Me_2SO_4, (92%).

SCHEME 4. Failed Addition−Elimination Reaction with 2a



even when the particularly reactive allylmagnesium bromide was used. Suspecting that deprotonation to form the metalloenamine was the problem, **2a** was treated with methylmagnesium bromide and quenched with methyl iodide (Scheme 4). However, none of the methylated product **13** was observed. The poor reactivity of cyclic stannyl imidate **2a** with various organomagnesium reagents is unclear at this point. The presence of the (tributyl)tin moiety may decrease the electrophilicity of the imidate carbon by virtue of inductive electron donation, thus causing nucleophilic addition to be more difficult. Another explanation could be the formation of a pentacoordinate stannate complex such as **12**, which may be stable under the reaction conditions and hydrolyzed upon aqueous workup (Scheme 4).[8,9] Unfortunately, the more reactive alkyllithium species were not viable alternatives as a result of the extremely facile tin−lithium transmetalation reaction, which would form an undesired 2-azaallyllithium species. Other organometallic reagents, such as alkylzincs and organocopper reagents, were either less reactive than organomagnesium reagents[10] or were also incompatible with the tin moiety.

Thus an alternative approach was sought in which stannyl lactam **11** was converted into a more reactive

(6) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437−1441.

(7) (a) Pearson, W. H.; Stevens, E. P. *Synthesis*, **1994**, 904−906. (b) Katritzky, A. R.; Chang, H.-X.; Wu, J. *Synthesis* **1994**, 907−908.

(8) The formation of a pentacoordinate stannate complex has been verified experimentally and is proposed to be an intermediate in tin−lithium exchange in THF (see ref 9). See: (a) Reich, H. J.; Bevan, M. J.; Gudmundsson, B. O.; Puckett, C. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3436−3439. (b) Ashe, A. J., III; Lohr, L. L.; Al-Taweel, S. M. *Organometallics* **1991**, *10*, 2424−2431. (c) Maercker, A.; Bodenstedt, H.; Brandsma, L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1339−1341.

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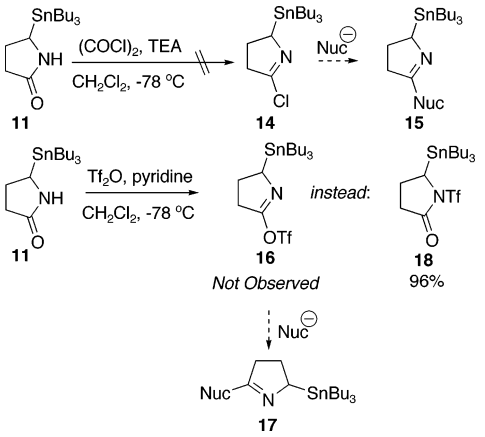
(10) The presence of the nitrogen in the *O*-methyl imidate leads to a much less electrophilic carbon at the imidate center compared to an ester. Thus rather reactive organometallic reagents would be required. For example, Smith showed that alkyllithium reagents are needed in order to add to simple cyclic *O*-methyl imidates: Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin, P. L. E. *J. Org. Chem.* **1984**, *49*, 4397−4399.

SCHEME 5. Attempts at Imidoyl Chloride and Imidoyl Triflate Formation



intermediate (Scheme 5). Initial efforts focused on forming an imidoyl chloride similar to those formed in the Vilsmeier−Haack reaction.[11] However, treatment of **11** with a variety of chlorinating reagents and acid scavengers all led to decomposition of the starting material (Scheme 5). A second option was to form an imidoyl triflate **16** from lactam **11**. A report by Charette disclosed the mild conversion of *acyclic* amides into imidoyl triflates and trapping with an amine to produce the desired amidine.[12] Unfortunately, using the conditions reported, only the formation of *N*-triflated product **18** was observed. The similar imidoyl benzotriazole was not investigated because of the relatively harsh conditions for its formation and the tendency of organometallic reagents to attack the benzotriazole moiety.[13]

The strategy of using imidoyl chloride **14** and/or triflate **16** in transition metal catalyzed cross-coupling reactions[14] was also apparent to us. Our inability to generate these species (**14** and **16**) led us to consider other intermediates that could serve as cross-coupling partners. Numerous examples of *S*-methyl thioimidates participating in cross-coupling reactions with Pd(0) or Ni(0) catalysts have appeared in the literature.[15] However, all of these involved aromatic *S*-methyl thioimidates, indicating that the C−S bond of **2b** may not be suitably activated for the oxidative addition/transmetalation sequence to occur. However, a report of a copper-mediated Pd(0)-catalyzed thioester cross-coupling reaction by Liebeskind[16] prompted us to explore a similar coupling with **2b**.

Initial examination of the cross-coupling reaction of thioimidate **2b** with phenylboronic acid using 1 mol % of Pd_2dba_3, 1.6 equiv of copper(I) thiophene carboxylate (CuTC), and 3 mol % of trifurylphosphine (TFP) in deoxygenated THF at 50 °C led only to decomposition of the starting stannane in which the (tributyl)tin moiety was removed (Table 1, entry 1). This result was not wholly unexpected since Falck and co-workers have shown that Cu(I) salts efficiently transmetalate with stannanes to generate the corresponding organocopper reagents.[17] Performing the reaction without CuTC led only to recovered starting material (entry 2). At this point it became apparent that thioimidate **2b** was not reactive enough to participate in these relatively mild coupling conditions.

Previously, Casalnouvo and co-workers reported the successful Pd(0)-catalyzed coupling of the more reactive benzylzinc bromide with 2-(methylthio)benzothiazole in good yields.[15l] It was thought that the use of the more reactive alkylzinc reagents would help facilitate the transmetalation sequence enabling the coupling reaction to proceed. Thus treatment of thioimidate **2b** with benzylzinc bromide and palladium tetrakis(triphenyl)-phosphine in THF at 60 °C gave a 45% yield of 5-benzyl-2-(tributylstannyl)-3,4-dihydro-*2H*-pyrrole **20** (entry 3). Unfortunately, **20** was also accompanied with a 45% yield of benzyl(tributyl)tin. All attempts to minimize this side

(11) For reviews, see: (a) Meth-Cohn, O.; Stanforth, S. P In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 777−794. (b) Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 485−599. (c) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659−3726. (d) Bonnett, R. in *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; Wiley-Interscience: New York, 1970; pp 597−662.

(12) (a) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1998**, *39*, 245−248. (b) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499−8502. (c) Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R. *Tetrahedron Lett.* **1998**, *39*, 711−714.

(13) For the synthesis of imidoylbenzotriazoles, see: Katritzky, A. R.; Stevens, C. V.; Zhang, G.-F.; Jiang, J. *Heterocycles* **1995**, *40*, 231−238. For a review of benzotriazoles as an auxiliary, see: Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683−2732.

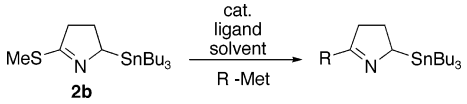
(14) For cross-coupling reactions involving imidoyl chlorides: (a) Lin, S.-Y.; Sheng, H.-Y.; Huang, Y.-Z. *Synthesis* **1991**, 235−236. (b) Kosugi, M.; Koshiba, M.; Atoh, A.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 677−679. (c) Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1985**, *26*, 3463−3466. (d) Rouden, J.; Bernard, A.; Lasne, M.-C. *Tetrahedron Lett.* **1999**, *40*, 8109−8112. (e) Ito, Y.; Inouye, M.; Murakami, M. *Chem. Lett.* **1989**, 1261−1264. For cross-coupling reactions involving sp^2-bound triflates, see: (f) Farina, V.; Krishnamurthy, V.; Scott, W. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, pp 1−633. (g) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. R. *J. Org. Chem.* **1993**, *58*, 5434−5444. (h) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040. (i) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

(15) (a) Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: New York, 1991; Vol. 3, pp 435−480. (b) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 2, pp 161−240. (c) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803−805. (d) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801−802. (e) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983−985. (f) Liebeskind, L. S.; Srogel, J. *Org. Lett.* **2002**, *4*, 979−981. (g) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304−9309. (h) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447−1450. (i) Tiecco, M.; Testaferri, L.; Tingoli, M. *Tetrahedron* **1983**, *39*, 2289−2294. (j) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 43−46. (k) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, *20*, 3425−3428. (l) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, *6*, 905−907.

(16) (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229−3231. For additional examples, see also: (c) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429−432. (d) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189−3192.

(17) The transmetalation was shown to be extremely facile when a coordinating heteroatom was present in the substrate allowing for coordination of the Cu(I) to help direct and stabilize the incoming Cu(I) salt; for leading references, see: Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982. For further examples of Cu−Sn transmetalation, see: (a) Bhatt, R. K.; Ye, J.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 3811−3814. (b) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2641−2643. (c) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065−2068. (d) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (e) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (f) Piers, E.; McEachern, E. J.; Burns, P. A. *Tetrahedron* **2000**, *56*, 2753−2765. (g) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609−3610. (h) Piers, E.; Gladstone, P. L.; Yee, J. G. K.; McEachern, E. L. *Tetrahedron* **1998**, *54*, 10609−10626. (i) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208−4209.

TABLE 1. Screening of Cross-Coupling Reactions with Thioimidate 2b[a]



entry	R-Met	cat./ligand	solvent	temp (°C)	time (h)	yield (%)	product
1	$PhB(OH)_2$	Pd_2dba_3 CuTC/TFP	THF	50	0.25	dec	**19**
2	$PhB(OH)_2$	Pd_2dba_3 TFP	THF	50	18	nr	**19**
3	BnZnBr	$Pd(PPh_3)_4$	THF	60	22	45	**20**
4	BnZnBr	Pd_2dba_3 TFP	THF	60	40	nr	**20**
5	PhZnBr	$PdCl_2(PPh_3)_2$	$PhCH_3$	22	18	nr	**19**
6	PhZnBr	$PdCl_2$dppf	$PhCH_3$	50	24	nr	**19**
7	PhZnBr	$NiCl_2$dppe	$PhCH_3$	50	18	dec	**19**
8	PhZnBr	$NiCl_2$dppp	$PhCH_3$8	22	18	nr	**19**

[a] THF deoxygenated prior to use using freeze−pump−thaw method (3×). TFP = trifurylphosphine, CuTC = copper(I) thiophene carboxylate, dba = dibenzylidene acetone, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane.

reaction, such as varying the catalyst loading, substrate concentration, and temperature, failed. Presumably transmetalation with benzylzinc bromide occurs under the reaction conditions. This was supported by treating **2b** with benzylzinc bromide in THF at 60 °C, leading to the slow disappearance of starting material and concomitant formation of benzyl(tributyl)tin by GC−MS. Attempts to trap the resultant 2-azaallylzinc species with either *trans*-stilbene in a [3 + 2] cycloaddition or methyl iodide in a substitution reaction both failed. Switching to the more stable Pd_2dba_3 failed to give any reaction (entry 4). Attempts to utilize the less reactive phenylzinc bromide were unsuccessful with a variety of catalysts including the more reactive Ni(0) catalysts (entries 5−8). From the results with BnZnBr and $Pd(PPh_3)_4$ it appeared that oxidative addition was occurring; however, the transmetalation step appeared to still be sluggish. The literature contains numerous examples of the use of additives to speed up stubborn transmetalation steps, such as the so-called "copper-effect".[17d] However, on the basis of previous studies (vida supra) it appeared that the use of such additives often increases the destannylation of **2b** whether by transmetalation or some other process. Instead, use of more reactive catalysts and organometallic reagents was pursued.

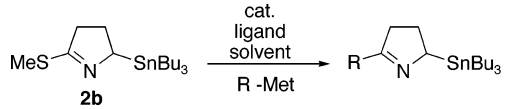
Having come full circle, we were once again faced with using organomagnesium reagents, this time to effect the transmetalation step. Work in the late 1970s by Kumada and co-workers had shown that sp^2 C−S and C−X bonds underwent smooth insertion of a Ni(0) catalyst and coupling with organomagnesium reagents.[18] Fortunately, our earlier work showed that organomagnesium reagents should not destannylate the stannyl thioimidate **2b** (vide supra). Treatment of stannyl thioimidate **2b** with 1.1 equiv of *n*-butylmagnesium chloride and 5 mol % of 1,3-bis(diphenylphosphino)propane nickel(II) chloride ($NiCl_2$-dppp) in diethyl ether (0.2 M) at 45 °C in a sealed tube led to a 12% yield of 5-butyl-2-(tributylstannyl)-3,4-dihydro-2*H*-pyrrole **21** (Table 2, entry 1). Lowering the temperature to 25 °C gave a 51% yield (entry 2), and a 67% yield was obtained when the reaction was performed at 0 °C (entry 3). Reaction temperatures lower than 0 °C gave lower yields (Table 2, entry 4). Initially, diethyl ether was used as solvent on the basis of reports that a less coordinating solvent (Et_2O vs THF) helped facilitate oxidative addition because of the lowered tendency of the catalyst to be deactivated by solvent coordination.[18] Although these results seemed to be borne out in our experiments, a small (∼10%) amount of destannylated material was consistently observed in these reactions. This was thought to be due to tin−metal transmetalation that is greatly facilitated in polar solvents.[19] Switching to the noncoordinating and less polar solvents toluene and methylene chloride provided much improved results. With $NiCl_2$dppp or $NiCl_2$dppe a dramatic improvement is observed using toluene, providing **21** in 80% yield (entries 5 and 6) compared to a 67% yield when ether is used (entry 3). However, other catalyst systems with toluene as solvent provided only inferior yields or no reaction (entries 7−11). In addition virtually no destannylated material could be observed by GC−MS when toluene was used as the solvent along with $NiCl_2$dppp or $NiCl_2$dppe. Use of methylene chloride as the solvent failed to give any reaction at all (entry 12). As a control, no reaction was observed when either the organomagnesium reagent or nickel catalyst was absent.

Using the optimized conditions (0.2 M in **2b**, 5 mol % catalyst, 1.1 equiv of RMgX in toluene) for the Kumada coupling various other organomagnesium reagents were also examined. Similar results were obtained with methylmagnesium chloride providing product **22** in 75% yield (Table 2, entry 13). Unfortunately, attempts to use secondary organomagnesium reagents such as isopropylmagnesium chloride led only to decomposition (Table 2, entries 15−19). The reason for the failure is uncertain, but it is known that compounds possessing sp^3-hybridized centers undergo β-elimination to generate metal hydride species. Apparently β-elimination is faster than reductive elimination with isopropylmagnesium chloride, whereas reductive elimination is as fast or faster than β-elimination for butylmagnesium chloride with the Ni(0) catalysts. Trost and others have utilized nickel hydride species, generated in situ from the reaction of isopropylmagnesium bromide and $NiCl_2(PPh_3)_2$ catalyst, for the reductive cleavage of sp^2 carbon−sulfur bonds.[20] Thus it is conceivable that a nickel hydride species is generated from β-hydride elimination, which reacts with **2b** leading

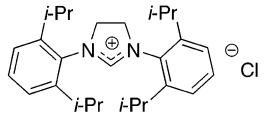
(18) For leading reference, see: Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958−1969.

(19) See ref 9e and also Grana, P.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 12511−12514.

TABLE 2. Kumada Coupling of Thioimidate 2b[a]



2b



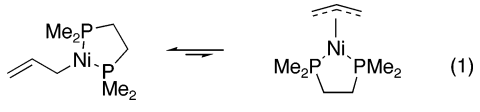
27

entry	R-Met	cat./ligand	solvent	temp (°C)	time (h)	yield (%)	product
1	BuMgCl	$NiCl_2$dppp	Et_2O	45	24	12	**21**
2	BuMgCl	NiC_2dppp	Et_2O	22	18	51	**21**
3	BuMgCl	$NiCl_2$dppp	Et_2O	0	18	67	**21**
4	BuMgCl	NiCldppp	Et_2O	−10	24	40	**21**
5	BuMgCl	NiCldppp	$PhCH_3$	22	0.25	80	**21**
6	BuMgCl	NiCldppe	$PhCH_3$	22	0.75	75	**21**
7	BuMgCl	NiCl,	$PhCH_3$	22	18	nr	**21**
8	BuMgCl	$NiCl_2(PPh_3)_2$	$PhCH_3$	22	18	nr	**21**
9	BuMgCl	$NiCl_2$dppt	$PhCH_3$	22	18	nr	**21**
10	BuMgCl	$PdCl_2$dppt	$PhCH_3$	22	18	22	**21**
11	BuMgCl	$Pd(Ph_3)_4$	$PhCH_3$	22	18	nr	**21**
12	BuMgCl	$NiCl_2$dppp	CH_2Cl_2	22	18	nr	**21**
13	MeMgCl	$NuCl_2$dppp	$PhCH_3$	22	0.25	75	**22**
14	MeMgCl	$NiCl_2$dppp	CH_2Cl_2	22	18	nr	**22**
15	*i*-PrMgCl	$NiCl_2$dppp	$PhCH_3$	22	18	dec	**23**
16	*i*-PrMgCl	$NiCl_2$dppp	CH_2Cl_2	22	18	dec	**23**
17	*i*-PrMgCl	$NiCl_2$	$PhCH_3$	22	18	dec	**23**
18	PrMgCl	$NiCl_2(PPh_3)$	$PhCH_3$	22	18	dec	**23**
19	PrMgCl	NiClzdppt	PhCH,	22	18	dec	**23**
20	BnMgCl	PdCldppf	PhCH,	22	18	dec	**20**
21	allylMgBr	$NiCl_2$dppp	PhCH,	22	0.25	31	**24**[c]
22	allylMgBr	$NiCl_2$dppp	$CHCl_2$	22	0.25	20	**24**[c]
23	allylMgBr	$Ni(acac)_2$, **27**	$PhCH_3$	22	0.33	dec	**24**[c]
24	allylMgBr	$Ni(acac)_2$, **27**	THF	22	0.5	dec	**24**[c]
25	allylMgBr	$NiCl_2$drnpe	$PhCH_3$	22	18	7	**24**[c]
26	allylMgCl	$PdCl_2$dppt	$PhCH_3$	0	1	dec	**24**[c]
27	PhMgBr	$NiCl_2$dppp	$PhCH_3$	22	1	35	**19**
28	PhMgBr	$NiCl_2$dppp[b]	$PhCH_3$	22	18	nr	**19**
29	PhMgBr	$NiCl_2$dppe	$PhCH_3$	22	0.25	36	**19**
30	PhMgBr	$PdCl_2$dppt	$PhCH_3$	22	4	55	**19**
31	1-propenyl-MgBr	$NiCl_2$dppp	$PhCH_3$	22	18	nr	**25**
32	vinylMgBr	$NiCl_2$dppp	$PhCH_3$	22	18	nr	**26**
33	vinylMgBr	$PdCl_2$dppt	$PhCH_3$	22	1	dec	**26**

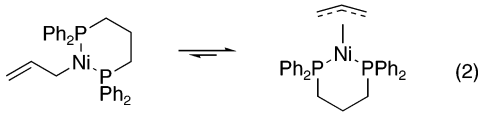
[a] Conditions: 0.2 M in stannane, 5 mol % catalyst, 1.1 equiv of R-Met. [b] Catalysts were preactivated with 10 mol % BuMgCl. [c] Migration of the alkene into conjugation occurred with all allyl Grignard reactions. dmpe = 1,2- bis(dimethylphosphino)ethane, acac = acetylacetonate, **27** = 1,3- bis(2,6-di- isopropylphenyl)imidazolium chloride.

to decomposition or cleavage of the C−S bond. Apparently, the product of reductive cleavage, if formed at all, is not stable to the reaction conditions. 2-(Tributylstannyl)-3,4-dihydro-2*H*-pyrrole (the proposed product of reductive C−S cleavage) was eventually synthesized but via the amine condensation method (bond disconnection b, Scheme 2) instead (vide infra).

Aryl and allyl organomagnesium reagents were also examined for reaction with thioimidate **2b** with limited success. Various experimental conditions were explored with allylmagnesium bromide (Table 2, entries 21−26). The best results were obtained by addition of 1.1 equiv of allylmagnesium bromide to a suspension of 5 mol % $NiCl_2$dppp and thioimidate **2b** in toluene (0.2 M) at 25 °C for 15 min (entry 21). Using these conditions a 31% yield of the allylated product **24** was obtained in which the alkene had migrated into conjugation with the imine. A survey of different ligands did not improve the yield or reaction rate. For example, using 1,3-bis(2,6-di-isopropylphenyl) imidazolium chloride **27** as the ligand (entries 23 and 24) led to complete decomposition of the starting material. In previous reports the 1,2-bis(dimethylphosphino)ethane (dmpe)[21] ligand has been shown to be the most effective ligand for coupling with allyl and vinyl organomagnesium reagents.[18] The proposed rationale being that more basic phosphine ligands such as dmpe help favor a conversion from a π-allylnickel complex **29** to the more reactive σ-bound allyl-nickel complex **28** (eq 1) through stabilization of the electron-deficient Ni(II) center by σ-donation from the phosphorus ligands; whereas less basic ligands such as 1,3-bis(diphenylphosphino)-propane (dppp) form a more stable five-coordinate π-allylnickel complex **31** (eq 2).[18] Unfortunately, in this instance the dmpe ligand failed to give any product (entry 25).



28 **29**



30 **31**

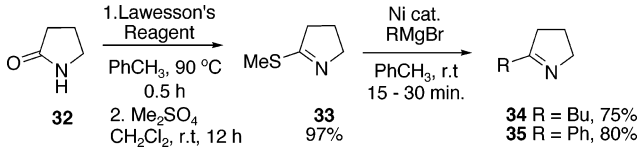
Likewise, under the conditions just mentioned, phenylmagnesium bromide gave a 35% yield of 5-phenyl-2-(tributylstannyl)-3,4-dihydro-2*H*-pyrrole **19** (Table 2, entry 27). However, the reaction was much slower, taking an hour rather than minutes to reach completion. It is well-known that an increase in the "bite-angle" created by the phosphine ligands, and the shorter Ni−C bonds can result in increased steric interactions at the coupling centers, which can dramatically increase the reaction rate.[22] The larger P−Ni−P angle created by the dppe ligand and hence smaller R−Ni−R′ angle may increase the steric interactions experienced by the pyrroline and the alkyl group helping facilitate reductive elimination. This observation appears to be borne out as a screen of various ligands revealed that the 1,3-bis(diphenylphosphino)ethane (dppe) ligand gave a much faster reaction time and comparable yields to the 1,3-bis(diphenylphosphino)propane (dppp) ligand (entry 27 vs 29). Surprisingly, use of $PdCl_2$dppf instead provided a 55% yield of **19** (entry 30).

(20) (a) Trost, B. M.; Ornstein, P. L *Tetrahedron Lett.* **1981**, *22*, 3463−3466. (b) Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1982**, *47*, 748−751. (c) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075−5090. (d) Fabre, J.-L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311−4314. (e) Cuvigny, T.; Fabre, J. L.; du Penhoat, C.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4319−4322. (f) Capet, M.; Cuvigny, T.; Penhoat, H.; Julia, M.; Loomis, G. *Tetrahedron Lett.* **1987**, *28(50)*, 6273−6276.

(21) For preparation of $NiCl_2$dmpe, see: Booth, G.; Chatt, J. *J. Chem. Soc.* **1965**, 3238−3241.

(22) (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163. (b) Saito, S.; Oh-Tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030.

SCHEME 6. Thioimidate Kumada Cross-Coupling



The reason for the relatively low yields observed with the allyl and aryl organomagnesium reagents as well as the complete absence of reaction with vinyl organomagnesium reagents (Table 2, entries 31−33) remains uncertain. However, the lower reactivity of the aryl and vinyl organomagnesium reagents compared to the alkyl organomagnesium reagents most likely means decomposition pathways may be able to compete with the desired reaction to drain off the starting materials. As mentioned earlier the allylmagnesium bromide may be forming a stable π-allylnickel complex that does not undergo cross-coupling with **2b**. In addition the presence of the inductively electron-donating (tributyl)tin group may slow the oxidative addition/transmetalation steps for the same reasons as discussed earlier for the addition−elimination reaction (Scheme 4).

During the early stages of development of the cross-coupling conditions, the known nonstannyl thioimidate **33**[23] was also investigated to examine the generality of the reaction for forming imines (Scheme 6). The optimized conditions for the cross-coupling of thioimidate **33** with organomagnesium reagents were found to be 5 mol % catalyst, 1.1 equiv of RMgX, and 0.2 M **33** in toluene. The known 5-butyl-3,4-dihydro-2*H*-pyrrole **34**[10] and 5-phenyl-3,4-dihydro-2*H*-pyrrole **35**[10] were obtained in 75% and 80% isolated yields, respectively. None of the pyrrolidine resulting from a second organomagnesium addition was seen in any of the cases examined. In comparison, the well-known alkyllithium addition to cyclic imidates is often plagued by bis-addition to give the pyrrolidine instead.[24] The nickel catalyst is required as no reaction is observed in its absence, leading to recovery of starting thioimidate **33**. The method developed provides an alternative to the current methods[25] for the generation of cyclic and acyclic imines.

With a series of novel cyclic (2-azaallyl)stannanes now in hand, the reactivity profile in 2-azaallyllithium and azomethine ylide cycloaddition reactions were investigated. Previous work has shown that acyclic 2-azaallyllithium species and azomethine ylides participate in cycloaddition reactions with a variety of alkenes to give substituted pyrrolidines.[1,2b,3−5] In addition, recent work has demonstrated that conjugated polyenes can also serve as efficient anionophiles.[26] The goal was then to examine if similar reactivity is observed with nonstabilized cyclic 2-azaallyllithiums derived from stannanes **19**, **21**, **22**, and **49**.

Stannane **21** was chosen as a representative 2-azaallyllithium precursor to probe the reactivity profile with various dipolarophiles (Table 3). *trans*-Stilbene **36** provided 2,3-diphenyl-7-azabicyclo[2.2.1]heptanes **43a/b** as a 1:1 mix of diastereomers in 87% yield. Structural assignment was made using the coupling constants observed with the lone bridgehead proton.[26] In a similar manner, reaction with phenyl vinyl sulfide **37** and phenyl vinyl selenide **38** gave the corresponding *endo* cycloadducts **44a/b** and **45a/b** in 43% and 74% yields, respectively, both as a 1:1 mix of diastereomers. An *endo*/*exo* assignment could not be made with the *trans*-stilbene adducts **43a**/**b** as a result of the nature of the dipolarophile, which masks the approach of the alkene in the transition state. Unfortunately, only decomposition products were observed when vinyltrimethylsilane **39** was used as the dipolarophile. The failure with vinyltrimethylsilane is somewhat surprising since the analogous reaction with acyclic 2-azaallyllithiums has been shown to proceed with moderate yields.[27] Rather surprising is the result observed when trimethyl(phenylethynyl)silane **40** was employed as the anionophile. No cycloadduct was observed; however, (2-azaallyl)silane **46** was recovered in 55% yield most likely as a result of desilylation by the 2-azaallyllithium intermediate.

The cyclic (2-azaallyl)stannanes were also shown to undergo [π6s + π4s] cycloaddition reactions with conjugated polyenes. Addition of *n*-butyllithium to a solution of cycloheptatriene **41** and stannane **21** yielded the [π6s + π4s] cycloadduct **47a** and the cyclic imine **47b** (1:1) in 67% combined yield (Table 3). The tricyclic amine **47a** was formed exclusively as the *endo*-adduct with the structural assignment being based on comparison of the coupling constants observed with similar compounds previously reported.[26a] In addition, reaction of stannane **21** with cyclohexadiene **42** provided the *endo*-cycloadducts **48a/b** as a 1.5:1 mix of double bond regioisomers in 68% combined yield. Both results are in accord with previous findings using conjugated polyenes in the 2-azaallyllithum cycloaddition reactions.[26b]

It should also be mentioned that, unlike the butyl- and methyl-substituted stannyl imines **21** and **22**, the phenyl-substituted imine **19** produced 1,2,3-triphenyl-7-azabicyclo-[2.2.1]heptane **50** as the sole product in 40% yield when reacted with *trans*-stilbene **36** (Table 4). The reason for the diastereoselectivity with imine **19** may be attributed to a steric clash between the bridgehead phenyl and one of the phenyls on *trans*-stilbene in the transition state. All attempts with **24** (Table 2, entry 21) in these cycloaddition reactions led only to decomposition. The reason for the failure is unclear at this point since

(23) Anbazhagan, M.; Dixit, A. N.; Rajappa, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2421−2424.

(24) See ref 10 and (a) Neilson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons, Ltd.: New York, 1991; Vol. 2, pp 425−483. (b) Bielawski, J.; Brandange, S.; Lindblo, L. *J. Heterocycl. Chem.* **1978**, *15*, 97−99. (c) Dudek, V.; Kvan, L. *Collect. Czech. Chem. Commun.* **1965**, *30*, 2472−2474. (d) Lukes, R.; Cerny, M. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2886−2890. (e) Cervinka, O. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1146−1150.

(25) Some examples include (a) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682−3684. (b) Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751−754. (c) Padwa, A.; Gasdaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027−1035. (d) Hoffman, R. V.; Buntain, G. A. *J. Org. Chem.* **1988**, *53*, 3316−3321. (e) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523−2530. (f) Kondo, T.; Okada, T.; Mitsudo, T. *J Am. Chem. Soc.* **2002**, *124*, 186−187. (g) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228−234. (h) Keppens, M.; deKimpe, N.; Stevens, C. *Tetrahedron Lett.* **1993**, *34*, 4693−4696. (i) Keppens, M.; deKimpe, N.; Fonck, G. *Synth. Commun.* **1996**, *26*, 3097−3102 and references therein.

(26) (a) Pearson, W. H.; Mans, D. M.; Kampf, J. W. *Org. Lett.* **2002**, *4*, 3099−3102. (b) Pearson, W. H.; Mans, D. M.; Kampf, J. W. *J. Org. Chem.* **2004**, *69*, 1235−1247.

(27) See refs 1b and 2b and Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345.

TABLE 3. Cycloaddition Reaction of Alkenes with Cyclic Stannane 21

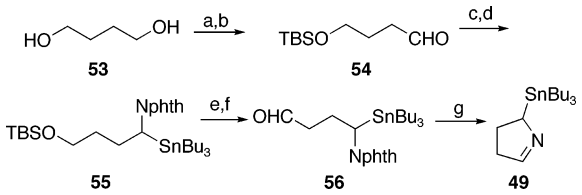
Stannane \ Alkene	Ph, Ph **36**	SPh **37**	SePh **38**	TMS **39**	Ph—≡—TMS **40**	**41**	**42**
Bu, N, $SnBu_3$ **21**	NH, Bu, Ph, Ph + NH, Bu, Ph, Ph **43a/b** 87% (1:1)	NH, Bu, SPh + NH, Bu, SPh **44a/b** 43% (1:1)	NH, Bu, SePh + NH, Bu, SePh **45a/b** 74% (1:1)	Decomp.	Bu, N, TMS **46** 55%	NH, Bu + Bu, N **47a/b** 67% (1:1)	NH, Bu + NH, Bu **48a/b** 68% (1.5:1)[a]

[a] Isolated as the picrate salt.

TABLE 4. Cycloaddition of *trans*-Stilbene with Stannanes 19, 22, and 49

Alkene \ Stannane	Ph, N, $SnBu_3$ **19**	Me, N, $SnBu_3$ **22**	N, $SnBu_3$ **49**
Ph, Ph **36**	NH, Ph, Ph, Ph **50** 40%	NH, Me, Ph, Ph + NH, Me, Ph, Ph **51a/b** 89% (1:1)	NH, Ph, Ph **52** 36%

SCHEME 7. Synthesis of Stannyl Imine 49[a]



[a] Conditions: (a) TBSCl, NaH, THF, 99%; (b) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 °C, 99%; (c) LDA, Bu_3SnH, THF, −78 °C; (d) phthalimide, DEAD, PPh_3, THF, 55% over 2 steps.; (e) AcOH/THF/H_2O (3:1:1), 75%; (f) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 °C, 91%; (g) H_2NNH_2, EtOH, reflux, 49%.

conjugated 2-azaallyllithium species have been shown to participate in the [3 + 2] cycloaddition reaction.[28]

In addition to using the cyclic alkyl-substituted (2-azaallyl)stannanes, 5-(tributylstannyl)-2-pyrroline **49**[29] was prepared to provide further insight into the chemistry of the cyclic stannanes. The synthesis of stannane **49** began with a McDougal protection[30] of 1,4-butanediol **53** followed by Swern oxidation to give known aldehyde **54**[31] (Scheme 7). Addition of aldehyde **54** to a solution of (tributyl)tinlithium, prepared from LDA and (tributyl)-tin hydride, produced a α-hydroxy stannane, which was immediately converted to the phthalimide **55** via Mitsunobu reaction.[2a] Silyl-deprotection under Corey conditions[32] followed by Swern oxidation[33] provided the condensation precursor **56**. Hydrazinolysis of **56** with hydrazine monohydrate under reflux in ethanol resulted in deprotection of the phthalimide followed by amine condensation to generate the cyclic imine **49**. Apparently concomitant hydrazone formation with the aldehyde under the hydrazinolysis conditions has a favorable enough equilibrium to allow formation of the cyclic imine. Unfortunately, attempts to prepare the homologous 2-(tributylstannyl)-2,3,4,5-tetrahydropyridine through the same route failed when attempting the hydrazinolysis/condensation sequence.

Treatment of stannane **49** with *trans*-stilbene **36** and *n*-butyllithium gave a 36% yield of the *endo* bicyclic amine **52** as a single diastereomer (Table 4). The lower yields obtained with imine **49** may be due to a greater inherent instability of the corresponding 2-azaallyllithium species enabling a greater proportion of the reactive anion to access alternate decomposition pathways compared to the 2-azaallyllithium species derived from stannanes **19**, **21**, and **22**. A valuable route to the tropane ring system could also be accessible via a higher-order cycloaddition reaction with a 6π-addend such as cycloheptatriene.[34] The resulting tricyclic amine could then be further transformed into cocaine analogues.[35] However, attempts to react stannane **49** with cycloheptatriene **41** were unsuccessful.

In addition to the 2-azaallyllithium cycloaddition reactions discussed above, the complimentary azomethine ylide cycloaddition manifold[36] was briefly investigated using electron-poor dipolarophiles. Heating a solution of imine **21** with methyl iodide and *N*-methylmaleimide at reflux in toluene for 18 h provided a 40% yield of the *endo* cycloadduct **57** as the sole product (Scheme 8). Similarly, use of the phenyl-substituted imine **19** gave only the *endo*

(28) See ref 3a,d and Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001−7004.
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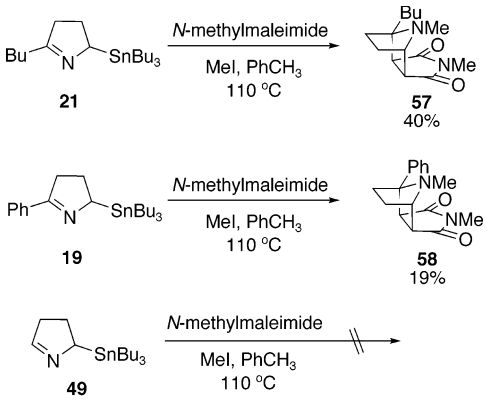
SCHEME 8. Azomethine Ylide Cycloaddition with Alkyl-Substituted (2-Azaallyl)stannanes



cycloadduct **58** in 19% yield. Unsubstituted imine **49** failed to give any products under the same conditions. To our knowledge these results are only the second reported use of completely nonstabilized endocyclic azomethine ylides in [3 + 2] cycloadditions. The other report comes from work by Pandey and co-workers in which a AgF-induced sequential double desilylation of *N*-alkyl-α,α′-bis(trimethylsilyl) cyclic amines generates nonstabilized cyclic azomethine ylides used in [3 + 2] cycloadditions to produce (*M*+3)-azabicyclo[*m*.2.1]alkanes.[37]

In summary, we have developed an efficient and novel transition-metal-catalyzed cross-coupling reaction between organomagnesium reagents and thioimidate **2b**. The reaction works well with primary alkyl organomagnesium reagents. In addition aryl and allyl organomagnesium reagents also participate in the cross-coupling reaction albeit in only moderate yields. The resultant cyclic alkyl-substituted (2-azaallyl)stannanes have also been shown to be viable precursors to the reactive 2-azaallyllithium species and azomethine ylides, which undergo [3 + 2] cycloaddition reactions with dipolarophiles to give exclusively the *endo* cycloadducts. These cycloadducts can serve as suitable starting points for further elaboration into biologically important bicyclic alkaloids.

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Supporting Information Available: Experimental procedures and ^{1}H and/or ^{13}C spectra for all new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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