ORGANIC LETTERS

2013
Vol. 15, No. 20
5358–5361

Tandem Isomerization and C–H Activation: Regioselective Hydroheteroarylation of Allylarenes

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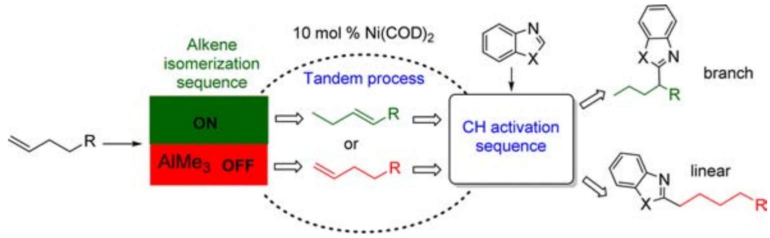
Received September 14, 2013

ABSTRACT



The first Ni-promoted prototype reaction based on the tandem C–H activation of heteroarenes with alkene isomerization is demonstrated, leading to the branched hydroheteroarylation products. Simultaneously, the reaction selectivity can be chemically switched to linear adducts through Ni–Al tandem catalysis.

Transition-metal-mediated C–H bond activation has emerged as a powerful synthetic tool, avoiding extra steps associated with prefunctionalized coupling partners. Surprisingly, only a few cases of such tandem processes[1] consisting of alkene isomerization and C–H bond activation are known. For example, Bergman and Ellman have observed olefin isomerization in the Rh-mediated synthesis of multicyclic pyridine and quinolone via intramolecular C–H bond functionalization.[2] Similarly, Willis exploited alkene isomerization in preparing indoles and benzofurans via palladium-mediated arylation of styryl units.[3] Moore also observed similar tandem process mediated by $Ru_3(CO)_{12}$ in carbonylation of pyridine.[4]

Nickel-promoted catalysis has been recognized as an attractive synthetic manifold because of its low cost and low toxicity.[5] Renowned examples of Ni promoted catalytic process are involved with olefin isomerization ranging from the production of linear α-olefins in the shell higher olefin process (SHOP)[6] to the hydrocyanation of butadiene by DuPont to prepare adiponitrile.[7] Nevertheless, catalytic C–H functionalization in a selective fashion facilitated by nickel catalysts still remains a great challenge,[8] despite the tremendous success of palladium catalysts for this purpose over the past years.[9]

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(1) Selected review papers on tandem reaction: (a) Haibach, M. C.; Kundu, S.; Brookhart, M.; Goldman, A. S. *Acc. Chem. Res.* **2012**, *45*, 947. (b) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432. (c) Hussain, M. M.; Walsh, P. J. *Acc. Chem. Res.* **2008**, *41*, 883. (d) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (e) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (f) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(2) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2978.
(3) Yagoubi, M.; Cruz, A. C. F.; Nichols, P. L.; Elliott, R. L.; Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 7958.
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(6) (a) Peuckert, M.; Keim, W. *Organometallics* **1983**, *2*, 594. (b) Peuckert, M.; Keim, W.; Storp, S.; Weber, R. S. *J. Mol. Catal.* **1983**, *20*, 115. (c) Keim, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 235.
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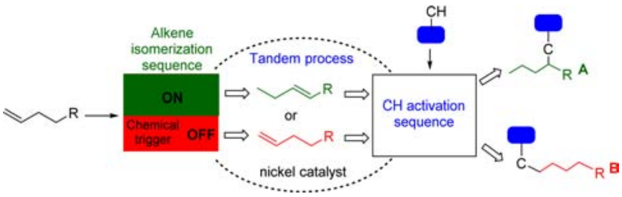
10.1021/ol402644y
Published on Web 10/02/2013

Scheme 1



In this context, we introduce a proof of principle to integrate olefin isomerization in a tandem manner with C−H bond activation promoted by only a single-component Ni catalyst (Scheme 1). We speculate that the tandem C−H activation/alkene isomerization process is possible if one of the reaction sequences is more facile than the other, ensuring independence of the two operating catalytic cycles. Conversely, a particular reactivity or product selectivity can be reversed from the similar tandem protocol if one of the facile reaction sequences can be delayed by chemical intervention. Herein, we unravel the first Ni-promoted prototype reaction based on hybridizing the C−H activation of heteroarenes with alkene isomerization of allylarenes, leading to the branched hydroheteroarylation products. Simultaneously, we are able to chemically toggle the reaction selectivity toward linear adducts by delaying the alkene isomerization process using a chemical trigger ($AlMe_3$).

With our previous experience in nickel-mediated C−H bond functionalization of pyridine and heteroarenes,[8g,i] we are quite optimistic that the alkene isomerization cycle should proceed relatively fast. First, we examined the isomerization process of allylbenzene **2a** in the presence of $Ni(COD)_2$

(8) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (c) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070. (d) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264. (e) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. (f) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (g) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (h) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964. (i) Shih, W.-C.; Chen, W.-C.; Lai, Y.-C.; Yu, M.-S.; Ho, J.-J.; Yap, G. P. A.; Ong, T.-G. *Org. Lett.* **2012**, *14*, 2046. (j) Clement, N. D.; Cavell, K. J.; Jones, C.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277. (k) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845. (l) Liu, S.; Sawicki, J.; Driver, T. G. *Org. Lett.* **2012**, *14*, 3744. (m) Doster, M. E.; Hatnean, J. A.; Jeftic, T.; Modi, S.; Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923. (n) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490. (o) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573. (p) Guihaumé, J.; Halbert, S.; Eisenstein, O.; Perutz, R. N. *Organometallics* **2012**, *31*, 1300. (q) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061. (r) Qu, G.-R.; Xin, P.-Y.; Niu, H.-Y.; Wang, D.-C.; Ding, R.-F.; Guo, H.-M. *Chem. Commun.* **2011**, *47*, 11140.

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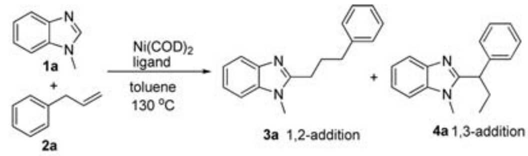
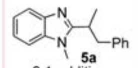
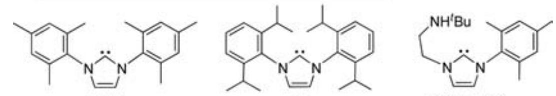
Table 1. Optimization of Reaction Conditions[a]



entry	ligand (equiv)	yield (%)[b]	3a:4a
1	bipyridine (0.1)	NR	-
2	1,10-Phen (0.1)	NR	-
3	PCy_3 (0.2)	27	15:85
4	IMes (0.1)	97	6:94
5	IPr (0.1)	80	36:64
6	Amino NHC (0.1)	88	9:91

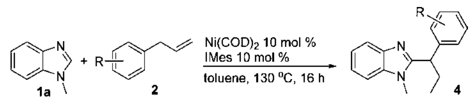
non-observed isomer

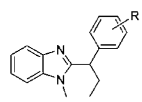
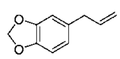
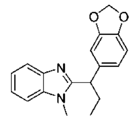
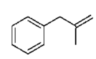
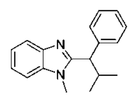




[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $Ni(COD)_2$ (0.05 mmol), and ligand in toluene (1 mL) at 130 °C for 16 h. [b] Isolated yield.

Table 2. Scope with Various Allylbenzenes: Branched Selectivity[a]



entry	2		major product	yield (%)[b]	3:4
1	2a	R = H		97	6:94
2	2b	R = *p*-Me		94	7:93
3	2c	R = *o*-Me		96	13:86
4	2d	R = *m*-Me		96	6:94
5	2e	R = *p*-OMe		65[c]	15:85
6	2f	R = *o*-OMe		75[c]	12:88
7	2g	R = *m*,*p*-$(OMe)_2$		55[c]	16:84
8	2h	R = *p*-CF_3		88	10:90
9	2i	R = *p*-F		69	12:88
10	2j			74	16:84
11	2k			73	58:42

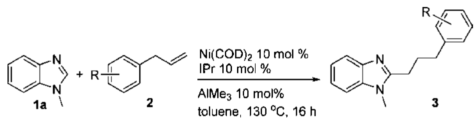
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $Ni(COD)_2$ (0.05 mmol), and IMes (0.05 mmol) in toluene (1 mL) at 130 °C for 16 h, unless otherwise noted. [b] Isolated yield (**3**+**4**). [c] $Ni(COD)_2$ (0.1 mmol) and IMes (0.1 mmol) were used.

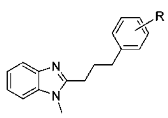
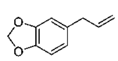
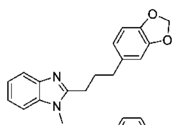
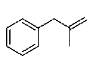
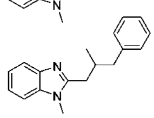
with various ligands in toluene upon heating (Table S1, Supporting Information).[10] It was promising to find that **2a** was exclusively isomerized to *trans*-*β*-methylstyrene within 1 h at 80 °C using 10 mol % of $Ni(COD)_2$ and IMes combination.[10] We next investigated the nickel-catalyzed hydroheteroarylation of **2a** with *N*-methylbenzimidazole **1a** with results summarized in Table 1. Nitrogen-containing ligands, such as bipyridine and 1,10-phenanthroline, were completely ineffective (entries 1 and 2). The use of PCy_3 gave a linear (**3a**) to branched (**4a**) product ratio of

(10) See the Supporting Information for further details.

15:85 in a 27% yield (entry 3). We found that N-heterocyclic carbene (NHC) ligands were very effective, giving over 80% yield (entries 4−6), and the use of IMes gave the best yield (97%, entry 4) with a high regioselectivity of linear and branched products (**3a**:**4a** = 6:94). It is worth mentioning that the other regioisomeric product **5a** was not observed, presumably due to rapid olefin isomerization.

Table 3. Scope with Various Allylbenzenes: Linear Selectivity[a]



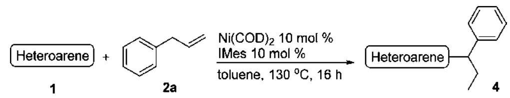
entry	2		major product	yield (%)[b]	3:4
1	**2a**	R = H		92	92:8
2	**2b**	R = *p*-Me		89	96:4
3	**2c**	R = *o*-Me		90	>99:1
4	**2d**	R = *m*-Me		88	>99:1
5	**2e**	R = *p*-OMe		81	>99:1
6	**2f**	R = *o*-OMe		89	98:2
7	**2g**	R = *m*,*p*-(OMe)$_2$		79	>99:1
8	**2h**	R = *p*-CF$_3$		33[c]	>99:1
9	**2i**	R = *p*-F		77	>99:1
10	**2j**			83	>99:1
11	**2k**			70	96:4

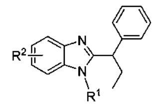
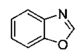
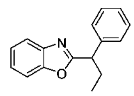
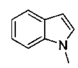
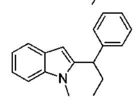
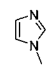
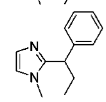
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), Ni(COD)$_2$ (0.05 mmol), IPr (0.05 mmol), and AlMe$_3$ (0.05 mmol) in toluene (1 mL) at 130 °C for 16 h, unless otherwise noted. [b] Isolated yield (**3**+**4**). [c] Ni(COD)$_2$ (0.1 mmol), IPr (0.1 mmol), and AlMe$_3$ (0.1 mmol) were used.

With the optimal reaction conditions in hand, myriad allylbenzene substrates were investigated to evaluate the generality of the reaction. The results are listed in Table 2. The substrates bearing electron-donating methyl substituents at the *ortho*-, *meta*- and *para*-positions afforded the corresponding branched products in excellent yields with high regioselectivity (∼9:1, entries 2−4). Moderate yields (∼60%) were witnessed for mono- or dimethoxy derivatives (entries 5−7) at different positions with a slight decrease of regioselectivity. The presence of strong electron-withdrawing substituents, such as *p*-fluoro and trifluoromethyl groups (entries 8 and 9), has no adverse effect on the regioselectivity, illustrating the nonsensitivity of the reaction toward electronic perturbation. Safrole (**2j**), a naturally occurring compound, is also suitable for this reaction with a high selectivity (entry 10). Hydroheteroarylation of (2-methylallyl)benzene (**2k**) gave an equal amount (∼1:1) of branched and linear regioisomers (entry 11). The lack of selectivity in **2k** may be due to the steric hindrance imposed by the extra methyl substitution on the olefinic moiety.

Decelerating the olefin isomerization sequence using a chemical trigger should in principle boost the selectivity toward the linear adduct **3**. To our delight, through the use of a more bulky IPr ligand with addition of 10 mol % AlMe$_3$,[10,11] the regioselectivity toward the linear product **3a** can be achieved in an excellent yield of 92% (entry 1, Table 3). Allylbenzenes bearing electron-donating groups (**2b**−**g**, entries 2−7) were also successfully converted to their corresponding linear (3-phenylpropyl)benzimidazole adducts with high yield and selectivity. The presence of an electron-withdrawing substituent like fluoride (**2i**) gave a good yield (77%), but the CF$_3$ group (**2h**) performed poorly (2h, 33%). Finally, a slight difference to the structural motif, such as in compounds **2j** and **k**, is also suitable for this reaction to afford the linear product.

Table 4. Scope with Various Heteroarenes: Branched Selectivity[a]



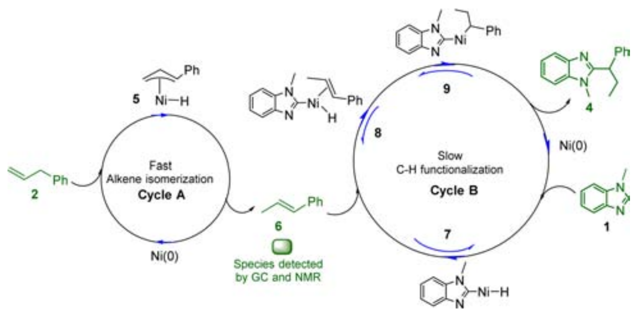
entry	1		major product	yield (%)[b]	3:4
1	**1a**	R^1 = Me, R^2 = H		97	6:94
2	**1l**	R^1 = (CH$_2$)$_7$CH$_3$, R^2 = H		86	8:92
3	**1m**	R^1 = CH$_2$-*o*-py, R^2 = H		76	8:92
4	**1n**	R^1 = CH$_2$Ph, R^2 = H		81	>1:99
5	**1o**	R^1 = *p*-C$_6$H$_4$Me, R^2 = H		94	>1:99
6	**1p**	R^1 = *o*-C$_6$H$_4$Me, R^2 = H		88	>1:99
7	**1q**	R^1 = *p*-C$_6$H$_4$OMe, R^2 = H		85	7:93
8	**1r**	R^1 = *p*-C$_6$H$_4$CF$_3$, R^2 = H		88	>1:99
9	**1s**	R^1 = Me, R^2 = 4/5-Me		92	>1:99
10	**1t**	R^1 = Me, R^2 = 5,6-Me$_2$		96	5:95
11	**1u**	R^1 = Me, R^2 = 4/5-OMe		84	8:92
12	**1v**			73	15:85
13	**1x**			58	>1:99
14	**1y**			45	>1:99

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Ni(COD)$_2$ (0.05 mmol), and IMes (0.05 mmol) in toluene (1 mL) at 130 °C for 16 h, unless otherwise noted. [b] Isolated yield (**3** + **4**).

To further demonstrate the catalytic utility of this protocol, we expanded the scope to a variety of benzimidazoles and other heteroarenes toward branched selectivity (Table 4). High branched selectivity and excellent yields were consistently observed with benzimidazoles bearing methyl (**1a**, entry 1), nonyl (**1l**, entry 2), pyridin-2-ylmethyl (**1m**, entry 3), and benzyl (**1n**, entry 4) at the nitrogen side arm. The substrates having electron-rich and electron-poor aryl substituents at nitrogen also proceeded well to afford high yield and regioselectivity (entries 5−8). Substitution at the benzene backbone did not interfere with the hydroheteroarylation process to give the branched products (entries 9−11). Azoles, including benzoxazole (**1v**), 1-methylindole (**1w**), and 1-methylimidazole (**1x**), also underwent hydroheteroarylation to afford branched selectivity with ease (entries 12−14), albeit with lower yields than those for **1a**. Again, the most striking feature and utility of this system is that inclusion of the chemical trigger

(11) Our previous work (ref 8i) on the styrene insertion into the C2−H bond of *N*-methylbenzimidazole revealed that addition of AlMe$_3$ can create a steric requirement to produce the linear product. However, the extra effect of AlMe$_3$ of slowing down the isomerization process still remained unclear at this stage.

Scheme 2. Proposed Mechanism



AlMe$_3$ completely switched the selectivity to linear **3** (see Table S3, Supporting Information).[10,11]

To gain preliminary mechanistic insights, we monitored the reaction process by GC analysis.[10] Detection of *trans*-β-methylstyrene **6** within a few minutes implied a fast isomerization process of **2a** to **6** with respect to the C−H bond activation of **1a** as shown in Figure S1.[10] Obviously, this key factor is responsible for the preferential formation of the branched product **4a** over the linear product **3a** in the absence of AlMe$_3$. A possible mechanism consisting of two operating catalytic cycles is proposed based on the results described above and the available literature: an alkene chain-walking isomerization mechanism[12] (Scheme 2, cycle A) and a C−H functionalization mechanism[8] (Scheme 2, cycle B). In the catalytic cycle A, **2a** is isomerized via a formal 1,3-hydride shift through a η^3-allyl Ni hydride intermediate **5**[12] to afford the more thermodynamically stable **6**. In the catalytic cycle B, the C−H functionalization process most likely proceeds through the following steps: (1) oxidative addition of the C−H bond to afford the Ni−H species **7**, (2) migratory insertion of **6** into the Ni−H to give **9**, and (3) reductive elimination of **9** to afford **4a**.[13]

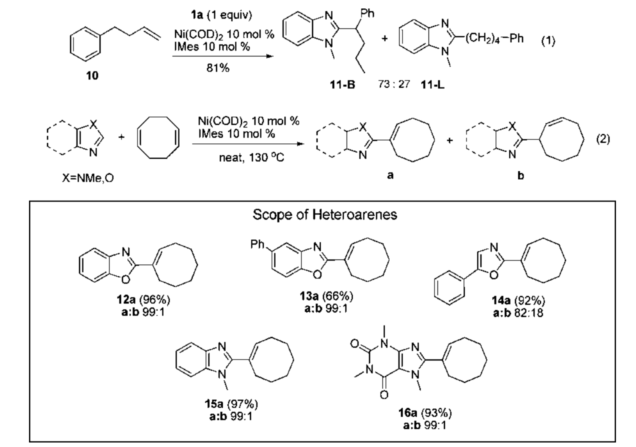
Encouraged by the successful tandem process in allylbenzenes, we speculate whether the viability of the tandem strategy may be applied to olefinic substrates other than allylbenzenes. Positively, olefin isomerization followed

(12) Oxidative addition of the allylic C−H bond to a metal, resulting in a π-allyl metal hydride intermediate, has been discussed to produce the isomerization product in the following selected literature. (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 4th ed.; John Wiley & Sons, Inc.: New York, 2005; pp 236−241. (b) Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819. (c) Biswas, S.; Huang, Z.; Choliy, Y.; Wang, D. Y.; Brookhart, M.; Krogh-Jespersen, K.; Goldman, A. S. *J. Am. Chem. Soc.* **2012**, *134*, 13276. (d) Scarso, A.; Colladon, M.; Sgarbossa, P.; Santo, C.; Michelin, R. A.; Strukul, G. *Organometallics* **2010**, *29*, 1487. (e) Parshall, G. W. *Homogeneous Catalysis*; Wiley-VCH: Weimheim, 1980; pp 31−35.

(13) The C−H bond cleavage and migratory insertion steps are believed to be reversible (see the Supporting Information for further details).

(14) It is noteworthy that formation of **12a** represented a redox neutral Heck-like coupling of heteroarenes via C−H bond activation, in which the second embedded olefin moiety in 1,5-cyclooctadiene acts as a hydrogen acceptor without using external oxidant. Our efforts utilizing a second embedded olefin moiety act as a hydrogen acceptor without using external oxidant will be the subject of a future manuscript.

Scheme 3



by hydroheteroarylation also occurred with 1-phenyl-3-butene **10**, demonstrating that an additional carbon does not interfere with the chain-walking of the double bond (Scheme 3, eq 1). We next examined a cyclic nonconjugated diene, 1,5-cyclooctadiene. The results were extremely encouraging (Scheme 3, eq 2). Treatment of 1,5-cyclooctadiene with benzoxazole in the presence of the Ni catalyst furnished the corresponding Heck-like product **12a** (96%) with a small amount of other isomeric product **12b** within 2 h. This consequence revealed the occurrence of both C−H bond activation of benzoxazole and isomerization of 1,5-cyclooctadiene. Similarly, the reaction scope can be applied to various heteroarenes like azole, benzimidazole and caffeine.[14]

In summary, we have demonstrated the first Ni-promoted regioselective hydroheteroarylation reaction incorporating alkene isomerization followed by the C−H activation of heteroarenes, leading to the branched selectivity. Simultaneously, we are able to deactivate the alkene isomerization to afford linear adducts by Ni−Al cooperative catalysis through steric control. Remarkably, such a tandem process can also be performed in a similar manner with 1,5-cyclooctadiene and 1-phenyl-3-butene to afford the corresponding coupling product. Further mechanistic investigations of this tandem C−H process and a broader scope are now the focus of our ongoing efforts.

Acknowledgment. We thank Professor Jennifer Scott (Royal Military College of Canada, Ontario, Canada) for her insightful suggestions for our work. We are also grateful to the Taiwan National Science Council (NSC: 101-2628-M-001-004-MY3) and Academia Sinica for their generous financial support.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.