

# ACCOUNTS of CHEMICAL RESEARCH<sup>®</sup>

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## Nickel-Catalyzed Intermolecular Domino Reactions

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### ABSTRACT

Nickel-catalyzed multiple-component reactions are a promising new type of domino reaction. For instance, a variety of starting materials such as alkenes, alkynes, and unsaturated carbonyl compounds can be connected with high selectivity under reasonably mild conditions. These reactions provide a new route to synthetically important key compounds including dienes, enynes, enol silyl ethers, and carbocycles. Furthermore, an asymmetric version of the reaction is successful. Thus, intermolecular domino reactions should be important reactions for years to come.

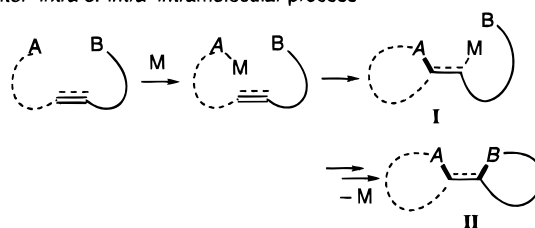
### Introduction

Domino reactions are organic reactions where multiple carbon-carbon bond formation is achieved in a single operation without any troublesome experimental procedures. The procedures are advantageous environmentally and economically and should have wide practical application.<sup>1-3</sup> In particular, intramolecular domino reactions are powerful methods for constructing complex organic molecules. On the other hand, intermolecular domino reactions with high selectivity are a challenging issue in synthetic organic reactions. A range of strategies involving the sequential generation of radical and anionic species are useful for such intermolecular transformations.<sup>4,5</sup> We have envisaged a new approach based on a transition-metal-catalyzed reaction.<sup>6</sup> This Account outlines nickel-

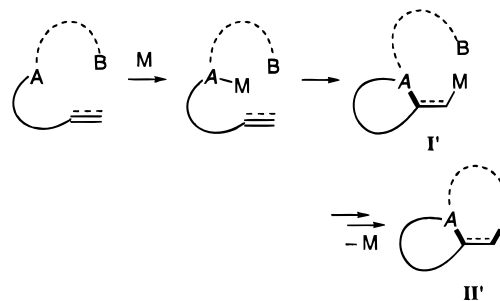
Shin-ichi Ikeda was born in Nagoya, Japan, on Oct 26, 1965. He received his B.S. (1988) and M.S. (1990) degrees from Gifu University, Japan. In 1993 he received his Ph.D. from Osaka University. After obtaining his Ph.D., he was an Assistant Professor at the Nagoya City University, Faculty of Pharmaceutical Sciences and was promoted to an Associate Professor in 1997. His research interests include the use of transition metal complexes as catalytic reagents in organic synthesis.

Scheme 1

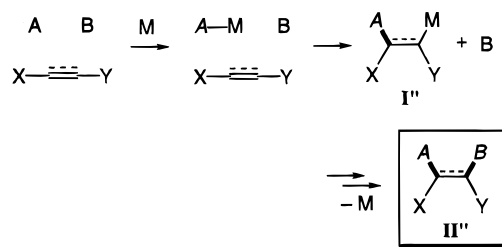
inter-intra or intra-intramolecular process



intra-inter or intra-intramolecular process



inter-intermolecular process



M = Pd, Ni, etc.

/ : newly formed C-C bond

catalyzed intermolecular domino reactions developed by our research group.

### Regio- and Stereoselective Intermolecular Domino Reaction

The use of a transition-metal-catalyzed reaction as part of a domino process has gained increasing interest. In particular, processes including the Mizoroki-Heck reaction, i.e., palladium-catalyzed arylation and alkenylation of unsaturated carbon molecules, are well-known ex-

Scheme 2

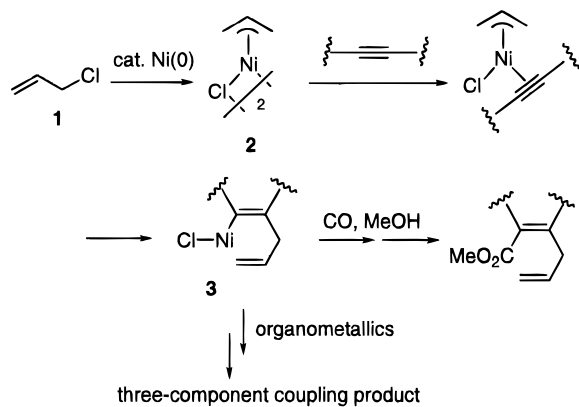
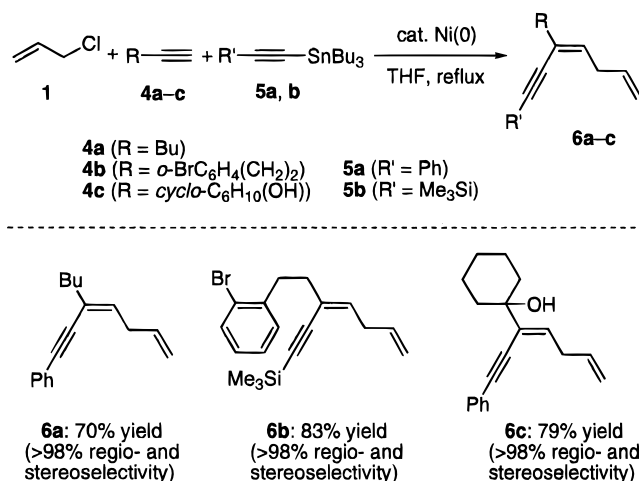


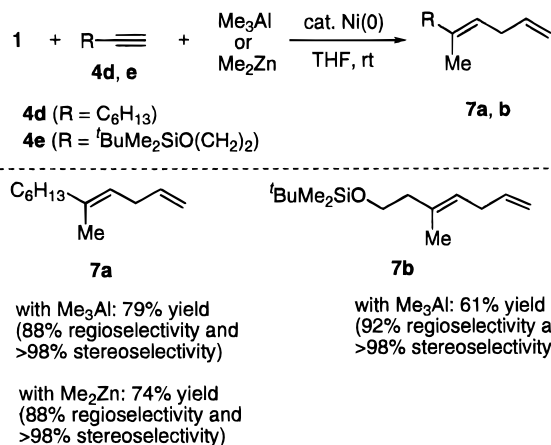
Chart 1



amples (Scheme 1).<sup>3,6</sup> These transformations proceed via the activation of a carbon unit (A) by a metal catalyst (M), e.g., oxidative addition to a Pd(0) complex, to generate an A–M species. The A–M species then adds to a carbon–carbon double or triple bond to lead to intermediate I or I', which is transformed into II or II' upon capturing another unit (B), e.g., coupling with carbon nucleophiles. In contrast to the domino process involving an intramolecular reaction, it would be difficult to develop a regio- and stereoselective intermolecular domino reaction of an unactivated alkene or alkyne with two independent carbon chains A and B.<sup>7–9</sup>

As an approach to intermolecular multiple-component domino coupling, we noted that a nickel(0) complex catalyzed the carbonylative coupling of allyl chloride 1 with an unactivated alkyne, carbon monoxide, and an alcohol (Scheme 2).<sup>10</sup> The key step is the preparation of alkenylnickel species 3 via the insertion of an alkyne into ( $\pi$ -allyl)nickel intermediate 2.<sup>11</sup> If 3 sequentially reacted with organometallics as carbon nucleophiles, a three-component coupling product would be obtained. Actually, the nickel(0)-catalyzed reaction of 1 with terminal alkynes 4 and alkenyltins 5 gave 6 with high regio- and stereoselectivities (Chart 1).<sup>12,13</sup> Dimethylzinc (Me<sub>2</sub>Zn) and trimethylaluminum (Me<sub>3</sub>Al) also reacted with 1 and 4 to give 7 (Chart 2).<sup>14</sup>

Chart 2



Scheme 3

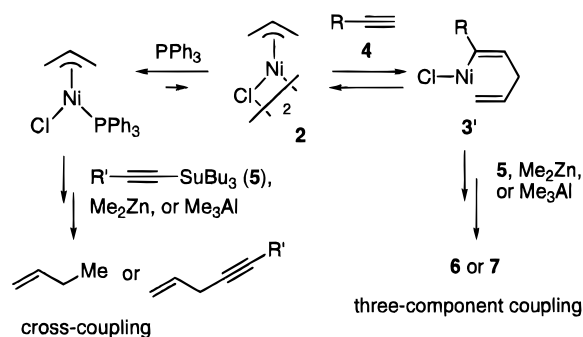
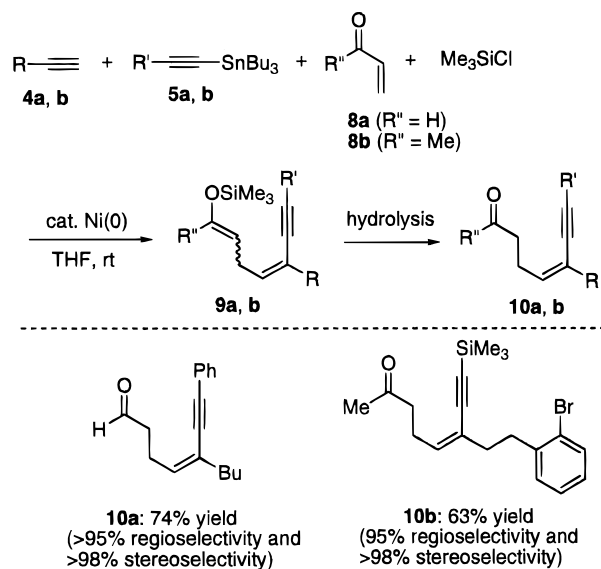


Chart 3



When an organophosphorus compound such as triphenylphosphine (PPh<sub>3</sub>) was added to the reaction system (1–2 equiv vs Ni(0) catalyst), cross-coupling of 1 and organometallics, rather than three-component coupling, took place preferentially.<sup>15</sup> This result indicates that the coordination of PPh<sub>3</sub> to 2 inhibits the production of 3' (Scheme 3).

Further investigations using enones 8 resulted in the development of a novel domino reaction. Alkynes 4 reacted with 5, 8, and chlorotrimethylsilane (Me<sub>3</sub>SiCl) in

Chart 4

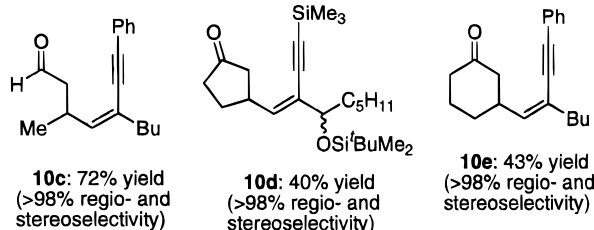
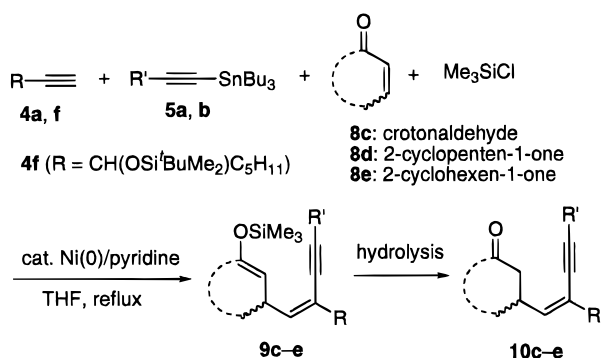
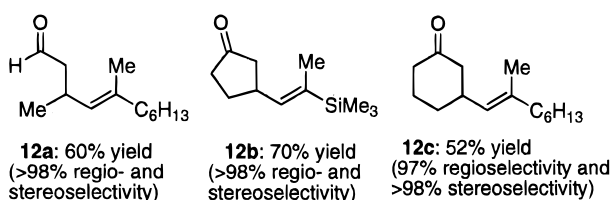
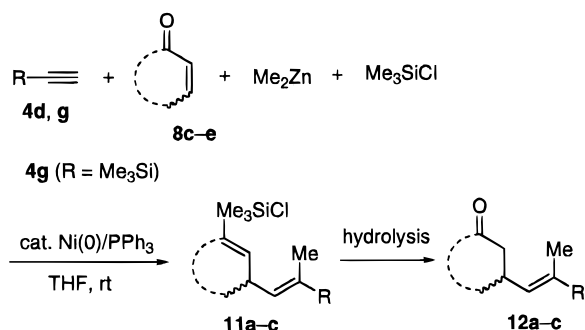
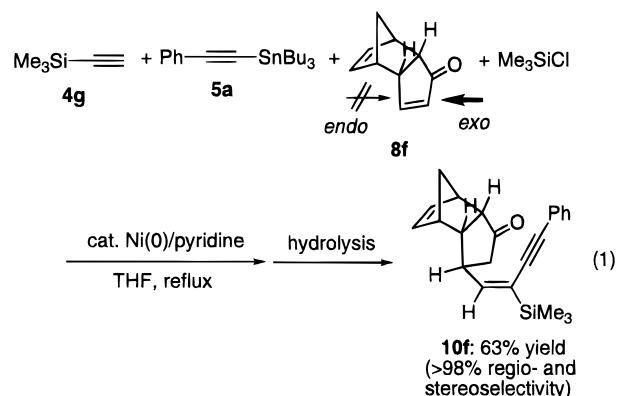


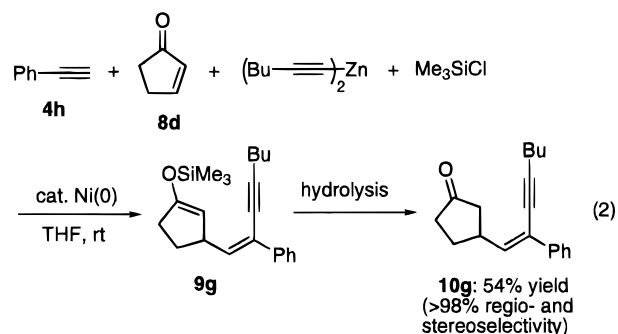
Chart 5



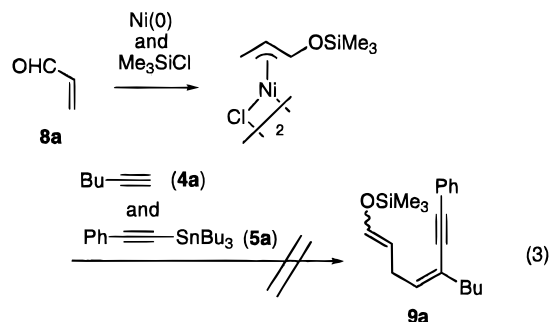
the presence of a nickel(0) complex to provide the four-component coupling products **9** (Chart 3).<sup>16</sup> The use of pyridine as an additive to the reaction medium was essential for the reaction with cyclic or  $\beta$ -substituted enones such as **8c–e** (Chart 4).<sup>17</sup> These reactions occurred with excellent regio- and stereoselectivities. On the basis of spectral analyses of the corresponding hydrolyzed products **10**, **8** was selectively introduced to the terminal carbon atom of a carbon–carbon triple bond in **4**, and an alkynyl unit of **5** reagent was added to the internal carbon atom. Both carbon units were added to **4** in a syn manner. Stereoselective construction of **10f** would result from the approach of the nickel catalyst from the *exo*-face of the cyclopentene unit in **8f** (eq 1).<sup>17</sup> While the domino coupling with 1-hexynyltin failed, bis(1-hexynyl)-zinc reacted with **8d** and **4h** to selectively give **10g** (eq



2).<sup>18</sup> A similar reaction using Me<sub>2</sub>Zn occurred in the presence of a Ni(0)/PPh<sub>3</sub> complex to give **11** (hydrolyzed products **12**) (Chart 5).<sup>19</sup>



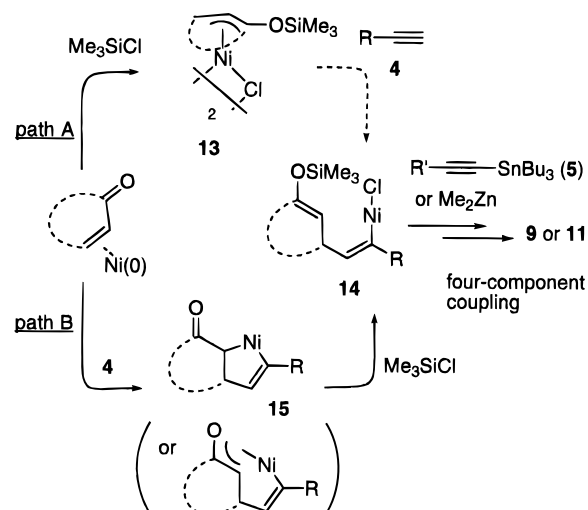
The regio- and stereoselective domino reaction using enones **8** might proceed via (i) generation of a ( $\pi$ -siloallyl)nickel species **13**, which is derived from the reaction of **8** coordinated to the nickel(0) species with Me<sub>3</sub>SiCl,<sup>20</sup> (ii) insertion of **4** into **13** to yield alkenylnickel intermediate **14**, and (iii) reaction with alkynyltins **5** or organozincs to give **9** or **11** (path A in Scheme 4). However, the stoichiometric reaction depicted in eq 3 did not give the corresponding **9a**. This result suggests that the reac-



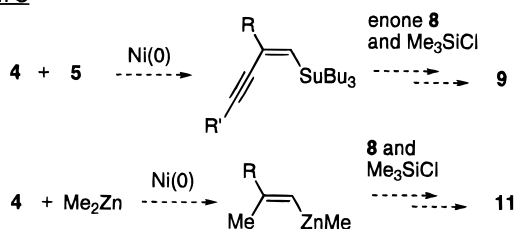
tion does not take place via path A. Therefore, an alternative route via **15** is proposed (path B). Although the addition of **5** or Me<sub>2</sub>Zn to **4** was not observed under these reaction conditions,<sup>21,22</sup> the possibility of another pathway (path C) via the conjugate addition of the alkenyltin or alkenylzinc species to **8** could not be excluded.<sup>23,24</sup>

As an intramolecular version of the domino coupling mentioned above, Montgomery et al. have reported the

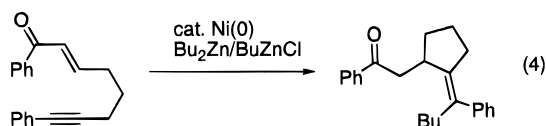
Scheme 4



path C

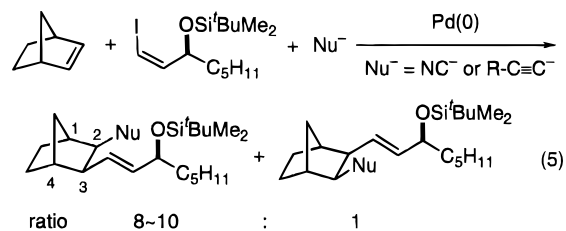


nickel(0)-catalyzed cyclization of alkynyl enones with organozincs (eq 4).<sup>25</sup>



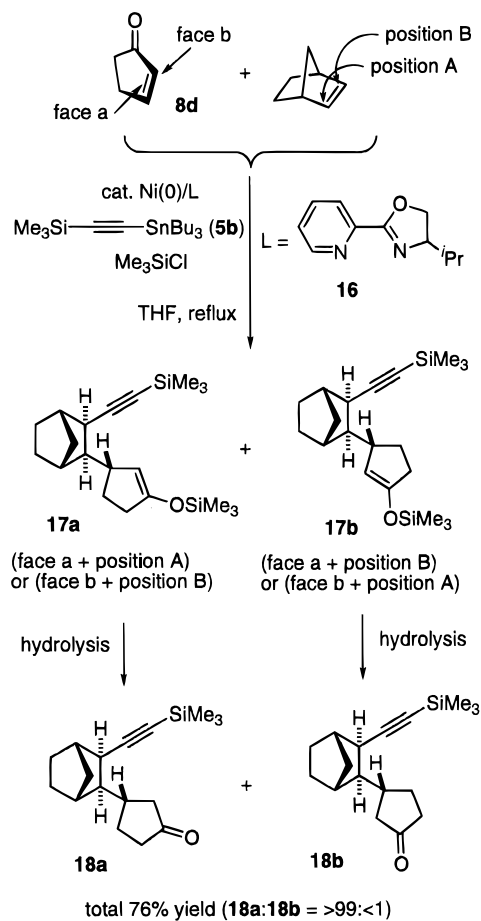
## Diastereodifferentiating Domino Reaction with Norbornenes

$C_5$ -symmetric molecules contain at least two prochiral centers, which can be converted to chiral carbons by appropriate enantiotopic functionalization.<sup>26</sup> Torii and co-workers reported that a Pd(0) complex catalyzed an asymmetric desymmetrization of norbornene (eq 5).<sup>27</sup> Use

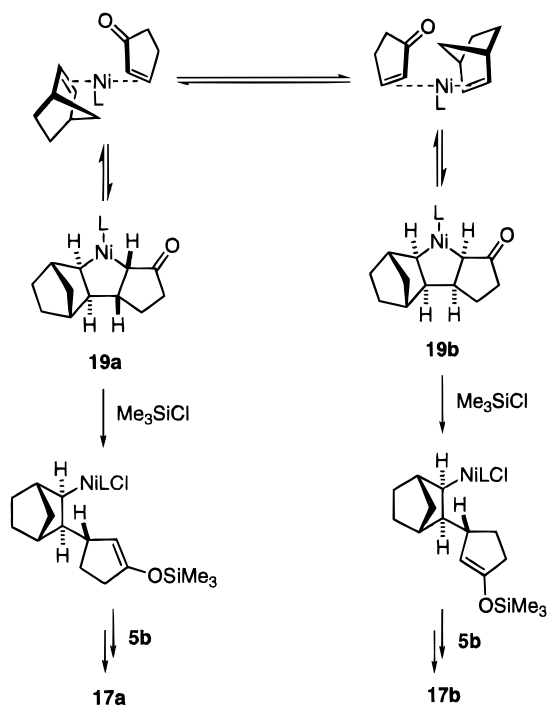


of a chiral-center-containing alkenyl iodide resulted in the differentiation of prochiral positions of the norbornene to create two chiral centers at C2 and C3. The combination of norbornene and a cyclic enone such as **8d**, which contains a prochiral face, should create a new domino process which is diastereodifferentiating. When **8d** was reacted with norbornene, an alkynyltin **5b**, and  $\text{Me}_3\text{SiCl}$  in the presence of nickel(0) species and a ligand **16**,<sup>28</sup> **18a** was obtained as a sole product after hydrolysis (Scheme 5).<sup>29</sup>

Scheme 5

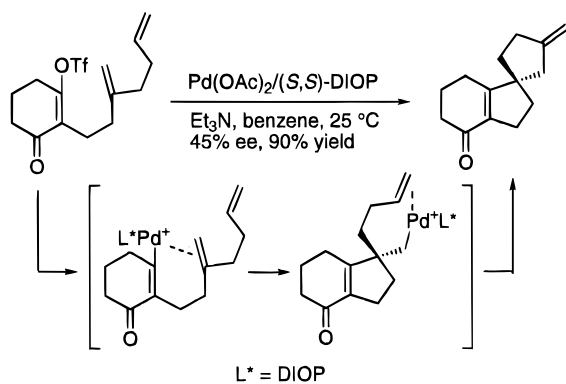


Scheme 6

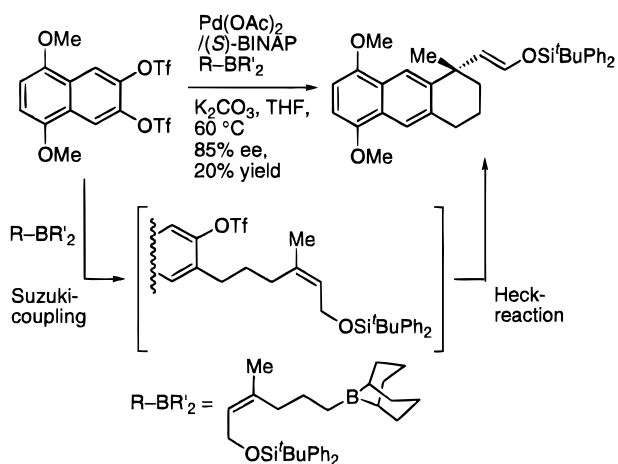


The diastereodifferentiation can be explained by the pathway outlined in Scheme 6. Initially, a mixture of both intermediates **19a** and **19b** is formed under kinetic control. The subsequent thermodynamic equilibrium

Scheme 7



Scheme 8



between **19a** and **19b** would control the coupling of one enantiotopic face of **8d** with the one enantiotopic position in norbornene. The reaction using **5b** occurred in THF under refluxing conditions. At that point, the equilibrium lies so far toward thermodynamically favored **19a** that it leads to the formation of **17a**.<sup>30</sup>

## Enantioselective Intermolecular Domino Reaction

The introduction of a catalytic reaction with asymmetric induction to a domino process is also an important theme in recent synthetic studies. Overman et al. reported the sequential cyclization of a polyene by an asymmetric Heck reaction (Scheme 7).<sup>31,32</sup> Enantioselection occurs in the first addition of the alkenylpalladium species to the alkenyl unit. The total asymmetric synthesis of (+)-xestoquinone by Key et al. has demonstrated the utility of this reaction.<sup>33</sup> Shibasaki et al. have provided an example of the process involving Suzuki coupling, i.e., palladium-catalyzed cross-coupling of organic electrophiles with organoboranes,<sup>34</sup> and the asymmetric Heck reaction (Scheme 8).<sup>35</sup> They also demonstrated the utility of an asymmetric Heck reaction–nucleophile (acetate, amine, and carbanion) capture process using an alkenyl triflate (Scheme 9).<sup>36,37</sup>

We have found a nickel-catalyzed asymmetric multiple-component coupling using  $\text{Me}_2\text{Zn}$  (see Chart 5).<sup>38</sup> Inter-

Scheme 9

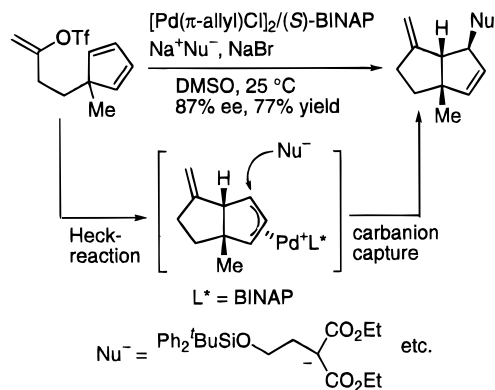
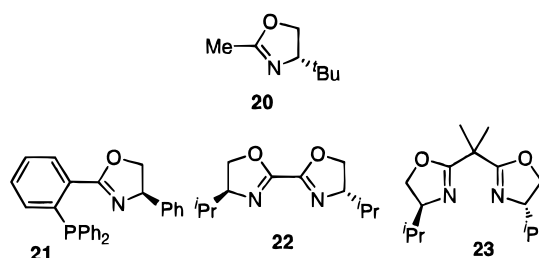
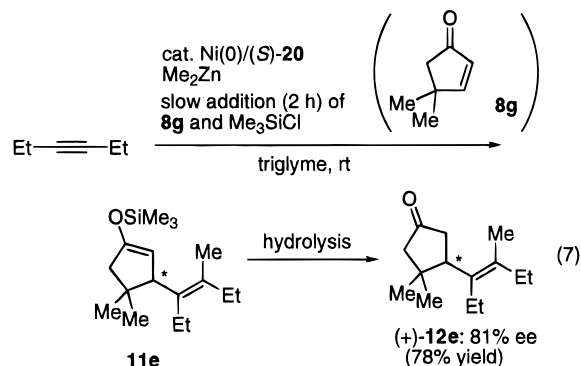
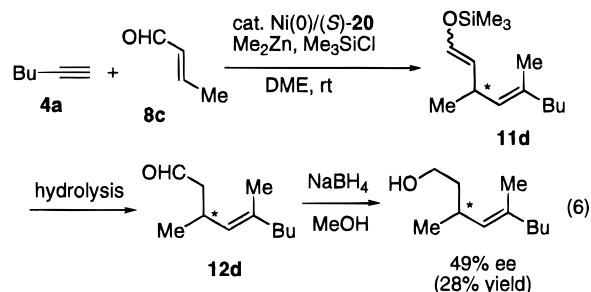


Chart 6



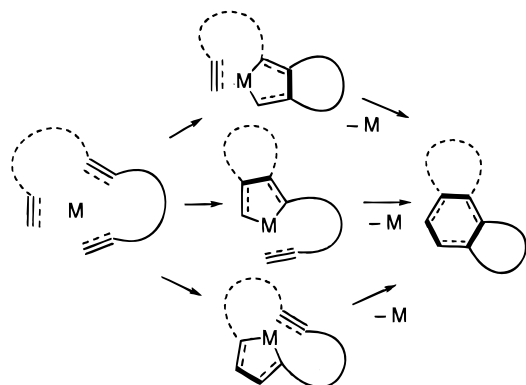
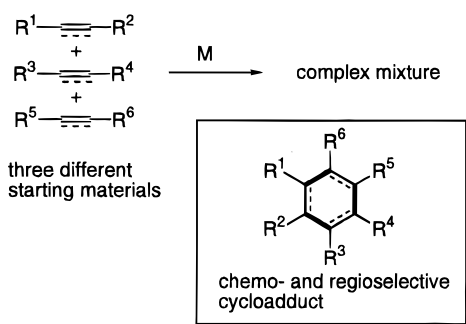
estingly, catalytic systems involving simple monodentate chiral oxazolines such as **20** (Chart 6),<sup>39</sup> which have been previously used as valuable chiral auxiliaries,<sup>40</sup> were very effective in giving optically active **12**. The results are summarized in eqs 6 and 7. In the reaction with an



internal alkyne such as 3-hexyne (eq 7), when a solution of **8g** and  $\text{Me}_3\text{SiCl}$  was slowly added to the reaction mixture including the catalyst, the corresponding **12e** was obtained in 81% ee (enantiomeric excess). In contrast, some optically active organophosphorus ligands such as BINAP<sup>41</sup> and MOP,<sup>42</sup> and bidentate oxazolines such as **21**–



Scheme 10

*intra- or partially intermolecular cyclotrimerization**completely intermolecular cyclotrimerization*

three different starting materials

chemo- and regioselective cycloadduct

M = Co, Ni, Ru, Rh, Pd, etc. / : newly formed C–C bond

**23**,<sup>40,43,44</sup> which have been extensively used as ligands for transition metals in asymmetric catalysis, did not give enantioselection.

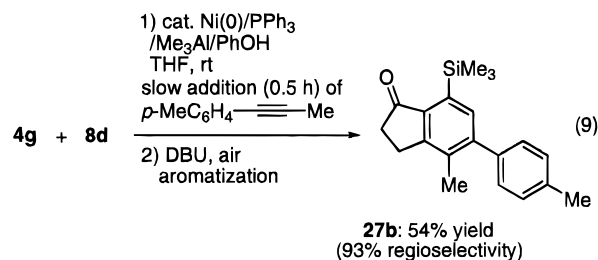
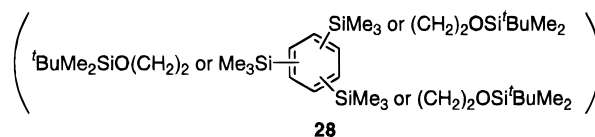
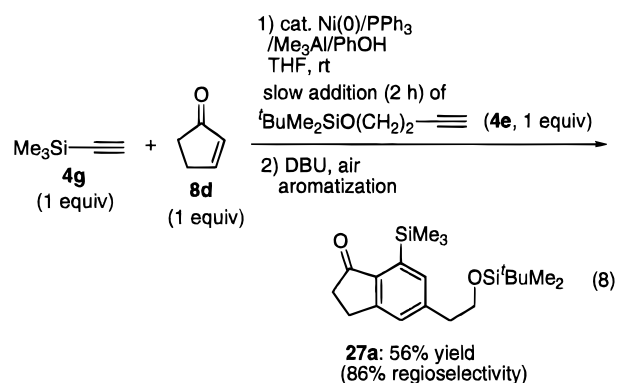
## Regioselective Three-Component Cyclotrimerization

Transition-metal-catalyzed cyclotrimerization (or [2 + 2] cycloaddition) leads to six-membered cyclic compounds with the formation of three new carbon–carbon bonds. Since the first example was reported by Reppe,<sup>45</sup> these reactions have been extensively studied by various research groups.<sup>46,47</sup> Whereas the intramolecular and partially intermolecular modes of the reaction have been used as efficient synthetic methods,<sup>48</sup> there is no known example of the completely intermolecular mode. The catalytic reaction usually leads to a complex mixture of cycloadducts, which severely limits its utility (Scheme 10).<sup>49</sup>

During our survey for domino coupling with alkynes **4** and enones **8**, we found that a binary metal system of nickel(0) and aluminum catalyzed a regioselective cyclotrimerization of one molecule of **8** and two molecules of **4** (Chart 7).<sup>50,51</sup> In this reaction, the  $\text{Me}_n\text{Al}(\text{OPh})_{3-n}$  ( $n = 0-2$ ) cocatalyst, which was generated from the reaction with  $\text{Me}_3\text{Al}$  and phenol in situ,<sup>52</sup> functions as a Lewis acid and activates enone **8**. The regiochemistries of the resulting cycloadducts **24** were determined by spectral analyses of

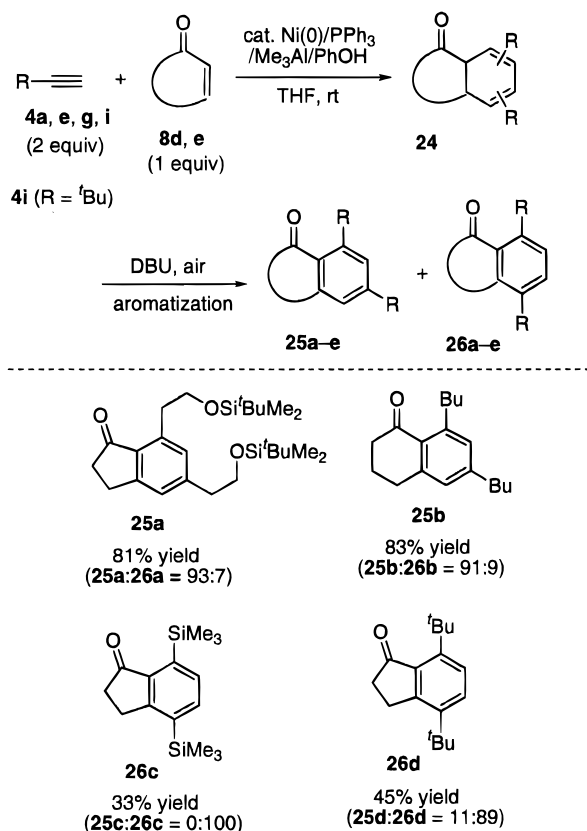
the corresponding aromatic compounds **25** and **26** produced upon subsequent treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in air. Interestingly, the regioselectivities in the formation of the products are dependent on the alkyne **4** used in the cycloaddition. Thus, the reaction with **4a** or **4e** tends to selectively give isomer **25**, while another isomer **26** is derived from the reaction with (trimethylsilyl)acetylene (**4g**) or *tert*-butylacetylene (**4i**).

Finally, we have developed the first catalytic cyclotrimerization of three different unsaturated molecules.<sup>53</sup> A three-component cycloadduct **27a**, in which the  $\text{Me}_3\text{Si}$  group is adjacent to the carbonyl group, was predominantly obtained when **4e** was added dropwise to a mixture of **8d** and **4g** in the presence of the nickel and aluminum catalytic system (eq 8). In this procedure, the production of undesired cycloadducts **25a**, **26c**, and **28** was suppressed. A biaryl product **27b** was synthesized from the reaction with an aryl-substituted internal alkyne (eq 9).

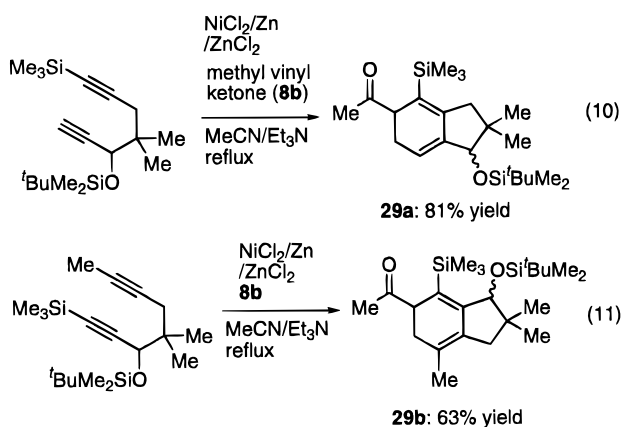


As a related example of a nickel-catalyzed and Lewis acid-assisted reaction, it has been shown that the cycloaddition of diynes and enones **8** proceeded in the presence of a combination of nickel and zinc.<sup>54</sup> In this reaction, trimethylsilyl-substituted diynes reacted with an equimolar amount of **8b** to give completely regiochemical-controlled cycloadducts **29**, in which the tri-

Chart 7



methylsilyl group is adjacent to the carbonyl group (eqs 10 and 11).<sup>55</sup>



## Conclusion

Intramolecular domino transformations are useful for synthesizing complex compounds. On the other hand, the development of synthetically useful intermolecular multiple-component domino reactions is in its infancy. The nickel-catalyzed reactions summarized in this Account are among the practical intermolecular multiple-component reactions that have been developed to date and should find wide application in synthesis.<sup>56</sup>

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