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Annulation of α,β-Unsaturated Imines and Alkynes via Cobalt-Catalyzed Olefinic C−H Activation

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ABSTRACT

A cobalt−triarylphosphine catalyst promotes an annulation reaction of an α,β-unsaturated imine and an internal alkyne to afford a polysubstituted dihydropyridine derivative in good yield under mild conditions. The reaction likely involves alkenylation of the olefinic C−H bond via cobalt-mediated nitrogen-assisted C−H activation followed by facile 6π electrocyclization of the resulting azatriene intermediate.

Over the past two decades, chelation-assisted C−H bond activation has emerged as a powerful strategy for the direct conversion of aromatic and heteroaromatic C−H bonds to new C−C bonds.[1] While not as extensive as the arene functionalization, this strategy has also been frequently practiced in the direct functionalization of olefins, with particular focus on the stereocontrolled synthesis of multisubstituted olefins via C−H alkylation[2] and arylation[3] reactions as well as the regiocontrolled synthesis of multisubstituted heterocycles via C−H alkenylation/cyclization cascades.[4−6] As an elegant example of the latter type of reaction, the group of Bergman and Ellman recently reported a cascade reaction comprising the rhodium(I)-catalyzed olefinic C−H alkenylation of an α,β-unsaturated imine with an alkyne and 6π-electrocyclization of the resulting azatriene intermediate.[4a,b] The dihydropyridine products are not readily accessible by other synthetic methods and are useful precursors to highly substituted pyridines and tetrahydropyridines. On the other hand, undesirable features of the reaction include the requirement of the noble metal catalyst with a tailored phosphine ligand and high reaction temperatures. We report here that a simple and inexpensive cobalt−triarylphosphine catalyst promotes the same type of cascade

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(6) For ruthenium catalysis, see: Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278.

10.1021/ol303259m

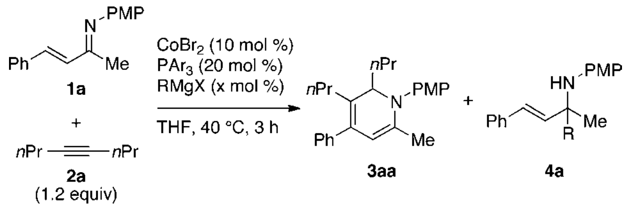
process, affording a series of dihydropyridine derivatives in moderate to good yields. The reaction represents a rare example of olefinic C$-$H functionalization reactions catalyzed by first-row transition metal complexes[3d,7] and features mild reaction conditions.

We recently developed an *ortho*-alkenylation reaction of aromatic imines with alkynes promoted by a quaternary catalytic system consisting of a cobalt(II) salt, triarylphosphine, Grignard reagent, and pyridine.[8] The present study began with an attempt to apply this catalytic system to the reaction of benzylideneacetone imine **1a** and 4-octyne **2a**, which met with only limited success. Thus, the reaction with $CoBr_2$ (10 mol %), $P(3\text{-}ClC_6H_4)_3$ (20 mol %), and $t\text{BuCH}_2\text{MgBr}$ (100 mol %) at 40 °C for 3 h afforded the annulation product, dihydropyridine **3aa**, in ca. 30% yield regardless of the presence (80 mol %) or absence of pyridine (Table 1, entries 1 and 2).

Subsequent screening of reaction conditions revealed a signifincant influence of the Grignard reagent. While Me_3SiCH_2MgCl and MeMgCl, which we have frequently used as the most effective reducing agents for cobalt-catalyzed C$-$H functionalization,[8,9] exhibited poor performances (entries 3 and 4), the use of *n*BuMgBr or a secondary alkyl Grignard reagent such as *i*PrMgBr and CyMgBr significantly improved the reaction (entries 5$-$7).[10,11] However, the reaction with these Grignard reagents was accompanied by a nonnegligible amount of a tertiary amine **4a** arising from Grignard addition to the C=N bond. Other chlorinated or fluorinated triarylphosphines gave rise to moderate or comparable catalytic activities (entries 8$-$10), while the reaction became rather sluggish with PPh_3 (entry 11). In either case, the adduct **4a** was obtained in 6$-$8% yield. Suppression of the formation of **4a** was achieved by reducing the loading of *i*PrMgBr from 60 mol % to 45 mol % without loss of the catalytic activity (entry 12). Thus, **3aa** was obtained in 87% yield (^{1}H NMR) and isolated in 59% yield due to partial decomposition during purification.

With the optimized catalytic system in hand, we explored the scope of the present annulation reaction (Scheme 1). First, various α,β-unsaturated imines were subjected to the reaction with diphenylacetylene. A variety of benzylideneacetone imines, except the one bearing an iodine atom, smoothly participated in the reaction to afford the adducts **3ab**$-$**3eb**, **3gb**, and **3hb** in good to excellent yields exhibiting tolerance for functional groups such as chloro, bromo, and cyano groups. Even the iodinated substrate afforded the annulation product **3fb** albeit in a low yield. The scalability of the reaction was demonstrated by the reaction of **1a** on a 5 mmol scale, which afforded the adduct **3ab** in 91% yield. Imines derived from other β-substituted and α,β-disubstituted enones also underwent annulation with diphenylacetylene, affording the products **3ib**$-$**3mb** in good yields. Note that, while most of the unsaturated ketimines existed as mixtures of *E*/*Z* isomers with respect to the C=N bond (ca. 9:1 to 3:2; see the Supporting Information), the dihydropyridine products were obtained near quantitatively in some cases (e.g., **3ib** and **3jb**). Considering that only the *E*-isomer is suitable for chelation-assisted olefinic C—H activation, isomerization of the C=N bond would have taken place readily under the reaction conditions. A cinnamaldehyde-derived imine was also amenable to the present reaction (see **3nb**).

Table 1. Screening of Reaction Conditions[a]



entry	PAr$_3$	RMgX (x)	yield (%)[b]	
			3aa	**4a**
1[c]	$P(3\text{-}ClC_6H_4)_3$	$t\text{BuCH}_2\text{MgBr}$ (100)	30	0
2	$P(3\text{-}ClC_6H_4)_3$	$t\text{BuCH}_2\text{MgBr}$ (100)	29	0
3	$P(3\text{-}ClC_6H_4)_3$	Me_3SiCH_2MgCl (100)	8	0
4	$P(3\text{-}ClC_6H_4)_3$	MeMgCl (100)	22	0
5	$P(3\text{-}ClC_6H_4)_3$	*n*BuMgBr (60)	67	6
6	$P(3\text{-}ClC_6H_4)_3$	*i*PrMgBr (60)	80	8
7	$P(3\text{-}ClC_6H_4)_3$	CyMgBr (60)	72	7
8	$P(4\text{-}ClC_6H_4)_3$	*i*PrMgBr (60)	45	6
9	$P(3\text{-}FC_6H_4)_3$	*i*PrMgBr (60)	71	7
10	$P(4\text{-}FC_6H_4)_3$	*i*PrMgBr (60)	75	7
11	PPh_3	*i*PrMgBr (60)	22	7
12	$P(3\text{-}ClC_6H_4)_3$	*i*PrMgBr (45)	87 (59)[d]	2

[a] The reaction was performed on a 0.2 mmol scale. PMP = 4-$MeOC_6H_4$. [b] Determined by GC or ^{1}H NMR. [c] Pyridine (80 mol %) was added. [d] Isolated yield.

Next, the reaction of **1a** with different alkynes was examined. With 1-phenyl-1-propyne, the reaction took place through preferential C$-$C bond formation on the 2-position to afford the adduct **3ac** as a major regioisomer with a regioisomer ratio of 85:15. On the other hand, the reaction of 1-phenyl-1-butyne resulted in a ca. 1:1 mixture of two regioisomers (see **3ad**). Such a trend in the regioselectivity is the same as the one observed in the cobalt-catalyzed aromatic C$-$H alkenylation.[8a,9e] Symmetrical diarylalkynes bearing *para*-methoxy and *meta*-bromo

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(7) (a) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

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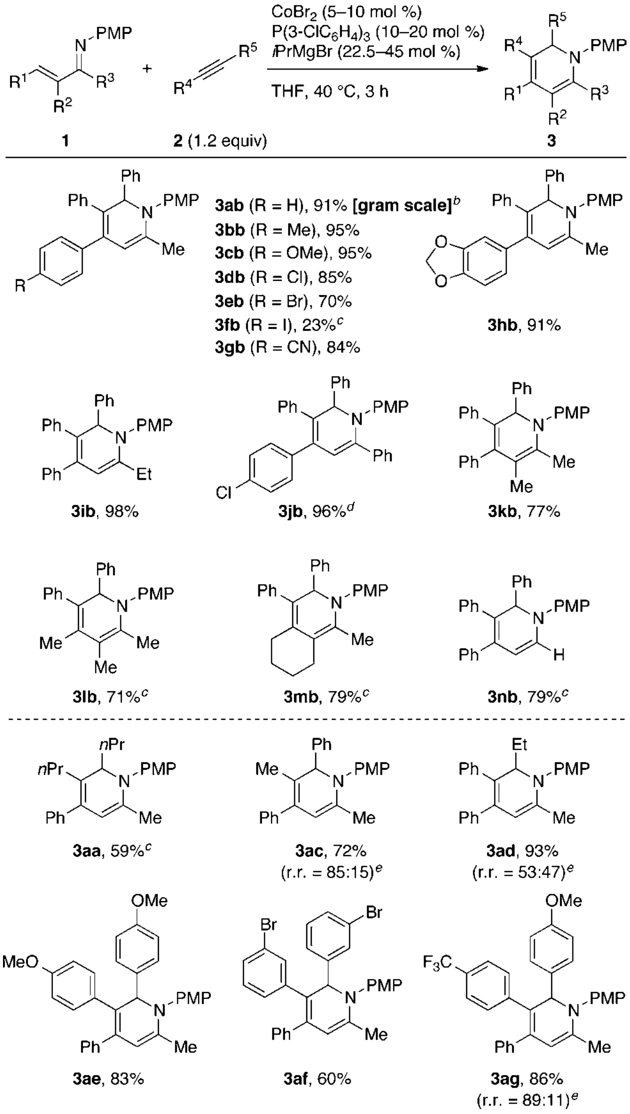
(10) (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (b) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (c) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(11) Such a significant effect of the Grignard reagent may indicate the formation of an alkylcobalt(0)ate species as a catalytically active species, while no evidence is available at this time (cf. ref 8a).

Scheme 1. Scope of α,*β*-Unsaturated Imines and Alkynes[a]

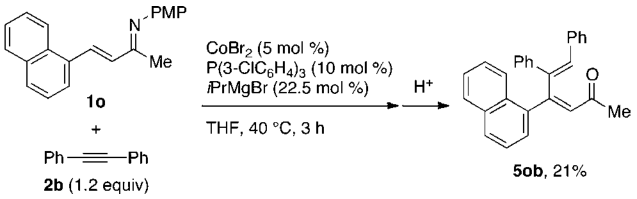


[a] Unless otherwise noted, the reaction was performed on a 0.2 mmol scale using 5 mol % of CoBr$_2$, 10 mol % of P(3-ClC$_6$H$_4$)$_3$, and 22.5 mol % of *i*PrMgBr. [b] 5 mmol scale. [c] The reaction was performed with 10 mol % of CoBr$_2$, 20 mol % of P(3-ClC$_6$H$_4$)$_3$, and 45 mol % of *i*PrMgBr. [d] Obtained as a mixture with a double bond isomer (5:1, see the Supporting Information). [e] r.r. = regioisomer ratio. The major isomer is shown.

groups afforded the adducts **3ae** and **3af** in 83% and 60% yields, respectively. An unsymmetrical diarylalkyne electronically biased by *para*-trifluoromethyl and *para*-methoxy groups preferentially afforded the regioisomer **3ag**, where the new C−C bond formed on the acetylenic carbon proximal to the *para*-trifluoromethylphenyl group. Origins of the regioselectivities for the unsymmetrical alkynes are discussed later.

When we subjected the imine **1o** bearing the 1-naphthyl group to the reaction with diphenylacetylene under the standard conditions, we obtained a dienone **5ob** rather than a dihydropyridine derivative (Scheme 2). Furthermore, when the reaction of **1a** and **2b** was subjected to acidic hydrolysis conditions (aqueous HCl) with a reaction time of 5 min, formation of a trace amount (< 1%) of the corresponding dienone was observed by GCMS. These observations suggest that the present annulation reaction proceeds in two steps, that is, cobalt-catalyzed olefinic C−H alkenylation and subsequent 6*π*-electrocyclization of the resulting azatriene derivative (vide infra). Note also that the reaction of **1a** and **2b**, when quenched with water with a reaction time of 5 min, afforded only **3ab** but no detectable amounts of the corresponding azatriene and dienone. This and the above results may further suggest that electrocyclization of the putative azatriene intermediate does not require the presence of the low-valent cobalt catalyst.

Scheme 2. Vinylic C−H Alkenylation of Imine **1o**



To gain insight into the relative reactivity of α,*β*-unsaturated imines, a competition experiment was performed (Scheme 3a). Thus, the reaction of an equimolar mixture of benzylideneacetone imine **1a** and cinnamaldehyde imine **1n** with diphenylacetylene **2b** (1.2 equiv) afforded the adducts **3ab** and **3nb** in 80% and 11% yields, respectively. This observation may be rationalized in terms of the conformational preference of the unsaturated imines. The ketimine **1a** would prefer to take the s-*cis* conformation, which is suited for the olefinic C−H activation, because of the allylic strain in the s-*trans* conformation (see the inset).[2a] On the other hand, there is no such allylic strain in the s-*trans* conformer of the aldimine **1n**. Next, the reaction of **1a** with a mixture of 4-octyne **2a** and diphenylacetylene **2b** exclusively afforded the adduct of the latter alkyne, **3ab**, in 64% yield (Scheme 3b). The same chemoselectivity was previously observed for the alkenylation of an aryl ketimine.[8a]

A proposed catalytic cycle of the present reaction is shown in Scheme 4. A low-valent cobalt species generated from the precatalyts undergoes nitrogen-assisted oxidative addition of the olefinic C−H bond to form a five-membered cobaltacycle intermediate.[12] As we proposed for the alkenylation of aryl ketimines,[8a] precoordination of the alkyne might be involved prior to the oxidative addition. Subsequent migratory insertion of of the alkyne is followed by reductive elimination to afford an azatriene intermediate, which readily undergoes 6*π* electrocyclization to furnish the dihydropyridine product. Considering that electrocyclization of azatriene often requires high temperatures,[13] it is notable that the present azatriene intermediate was not obtained under the mild conditions except for the

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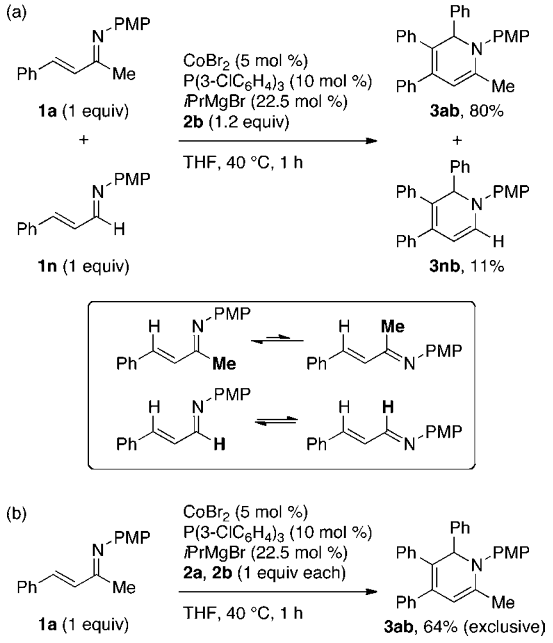
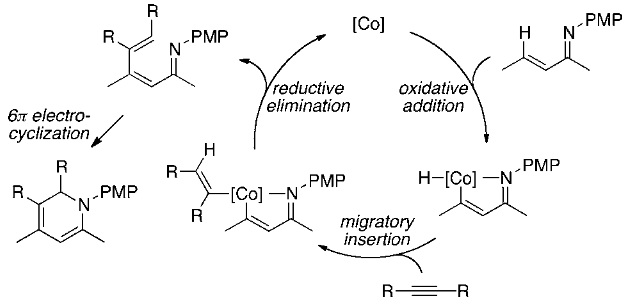
(12) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975.

Scheme 3. Competition Experiments



case shown in Scheme 2.[14] For this exceptional case, we speculate that steric repulsion between the 1-naphthyl and its neighboring phenyl groups has prevented the azatriene intermediate from taking on a cyclic conformation suitable for the electrocyclization. The regioselectivities observed for 1-phenyl-1-propyne (**3ac**) and 1-phenyl-1-butyne (**3ad**) are rationalized in terms of the propensity of the cobalt center to avoid steric repulsion during the alkyne insertion, while the regioselectivity for the unsymmetrical diarylalkyne (**3ag**) may be ascribed to the electrostatic nature of the putative alkenyl(hydrido)-cobalt species (i.e., Co(δ+)−H(δ−)).[15]

Scheme 4. Proposed Reaction Mechanism



In summary, we have developed a cobalt-catalyzed annulation reaction of an α,β-unsaturated imine and an internal alkyne that affords a dihydropyridine derivative in good yield under mild conditions. The reaction likely involves alkenylation of the olefinic C−H bond via cobalt-mediated C−H bond activation followed by 6π electrocyclization of the resulting azatriene intermediate. Further efforts to expand the scope of cobalt-catalyzed olefinic C−H bond functionalization are currently underway.

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

The authors declare no competing financial interest.

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[14] A possibility that the cobalt catalyst has assisted the cyclization step may not be fully excluded.

[15] NPA charges of the acetylenic carbon atoms of 1-methoxy-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene were calculated to be +0.027 (proximal to 4-methoxyphenyl) and −0.014 (proximal to 4-(trifluoromethyl)phenyl) at the B3LYP/6-31G* level.