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Diastereoselective Pyrrolidine Synthesis *via* Copper Promoted Intramolecular Aminooxygenation of Alkenes; Formal Synthesis of (+)-Monomorine

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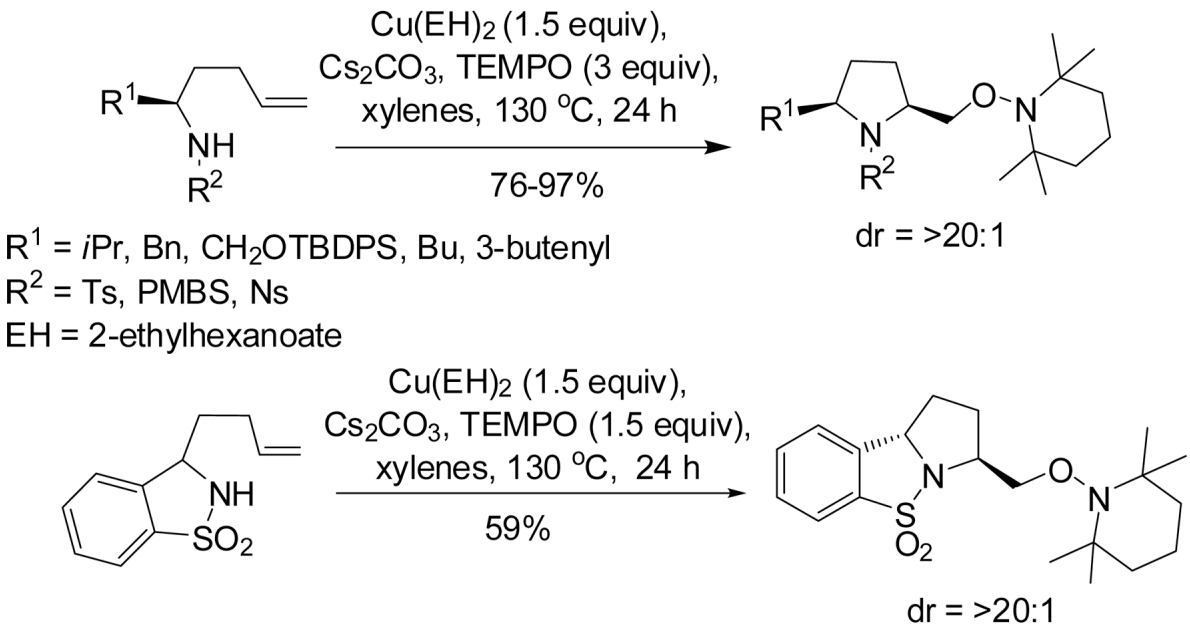
Abstract



The diastereoselectivity of the copper-promoted intramolecular aminooxygenation of various alkene substrates was investigated. α-Substituted 4-pentenyl sulfonamides favor the formation of 2,5-*cis*-pyrrolidines (dr >20:1) giving excellent yields which range from 76–97% while γ-substituted substrates favor the 2,3-*trans* pyrrolidine adducts with moderate selectivity (ca. 3:1). A substrate whose N-substituent was directly tethered to the α-carbon exclusively yielded the 2,5-*trans* pyrrolidine. The synthetic utility of the method was demonstrated by a short and efficient formal synthesis of (+)-monomorine.

Pyrrolidine moieties are frequently found in biologically active molecules.[1] These include glycosidase inhibitors such as alexine[2] and australine,[3] antiviral agents such as preussin,[4] antileukemia agents such as harringtonine[5] and crambescidin[6] and the angiotensin-converting enzyme (ACE) inhibitor ramipril.[7] Due to the therapeutic importance of these pyrrolidine alkaloids, considerable effort has been devoted to the stereoselective synthesis of substituted

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pyrrolidines.[8] In this paper, we report a copper(II) promoted diastereoselective synthesis of disubstituted pyrrolidines *via* an intramolecular aminooxygenation of alkenes.

The intramolecular aminooxygenation of alkenes can be catalyzed and promoted using a number of reagents and catalysts, but few result in the stereoselective synthesis of pyrrolidines.[9,10,11,12] Donohoe has reported a diastereoselective osmium-catalyzed aminohydroxylation that results in the synthesis of 2,5-cis-pyrrolidines.[9a] However, Donohoe's reaction requires two coordinating groups in the substrate, the sulfonamide nitrogen that forms the C-N bond, and an additional vicinal alcohol, to achieve high diastereoselectivity.

The diastereoselective copper-promoted aminooxygenation reactions reported in this paper do not require additional coordinating groups to provide high levels of 2,5-*cis*-pyrrolidine selectivity. Furthermore, analysis of the conformational factors that control the diastereoselectivity in these reactions led to the development of a 2,5-*trans*-pyrrolidine selective reaction as well (*vide infra*).

Recent reports from our group showed that the copper(II)-promoted synthesis of 2,5-disubstituted pyrrolidines *via* intramolecular alkene carboamination occur in high diastereoselectivity with predominating *cis* stereochemistry (Scheme 1).[13a] Mechanistic studies of these reactions[13a] revealed a pathway involving a primary carbon radical intermediate that was trapped efficiently with 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO), a standard carbon radical trapping agent (Scheme 1).[13b] These results led us to investigate the diastereoselectivity of this net alkene aminooxygenation reaction using substrates bearing substituents α as well as γ to the sulfonamide unit.

We first investigated the aminooxygenation reaction of 4-pentenyl sulfonamide **1** using catalytic amounts of copper(II) salts (Table 1).[11f, 11g] The use of the bisoxazoline ligand [(*R*, *R*)-Phbox] gave better conversion than the 2,2'-dipyridyl ligand under catalytic conditions using O_2 (1 atm) (Table 1, entries 1 and 2). The (*R*, *R*)-Phbox ligand and substrate **1** both favor formation of the C2(S) stereocenter (the reaction is matched).[11f] We have previously used these conditions to catalyze the aminooxygenation reactions of slightly more reactive achiral substrates.[11f,11g] However, neither reaction of sulfonamide **1** went to completion. While the catalytic reaction shows promise (yield = 60%, Table 1, entry 2), its optimization is ongoing. On the other hand, we were able to rapidly identify a highly efficient and operationally simple reaction process by use of a slight excess (1.5 equiv) of a readily available and inexpensive copper(II) carboxylate, copper(II) 2-ethylhexanoate [$Cu(EH)_2$]. Because $Cu(EH)_2$ is neither very expensive nor toxic and since the reaction is quite operationally simple, not requiring an O_2 atmosphere, we concluded that the stoichiometric reaction provides an acceptable solution until superior catalytic conditions are identified.

Copper(II) 2-ethylhexanoate is more reactive than many copper carboxylates owing to its high solubility in organic solvents.[13a, 14] Among the solvents (DMF, xylenes, CF_3Ph) and temperatures (120–160 °C) surveyed, we found that xylenes at 130 °C provided the optimal yield (94%, Table 1, entry 5). Slightly more than one equivalent of $Cu(EH)_2$ (1.5 equiv) was also required for optimal yield, and the reaction was complete within 24 h. Lower TEMPO amounts (1.5 equiv) gave slightly lower yield (entry 6), so the reactions were run using 3 equivalents of TEMPO.

Using the optimized reaction conditions (Table 1, entry 5), the reactions of a number of α and γ-substituted 4-pentenyl sulfonamides were examined (Table 2). Similar to the diastereoselectivity results in the analogous copper(II) promoted carboamination reaction of 4-pentenyl sulfonamides (Scheme 1), substrates **1, 3, 5, 7** and **9** generated the 2,5-*cis*-pyrrolidines **2, 4, 6, 8** and **10** in excellent yields with >20:1 selectivity (Table 2, entries 1–5). Gratifyingly, no hydroamination side products were observed in these reactions. The crystal

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structure of **2** indicated *cis* stereochemistry with an absolute configuration of C2(S), C5(R) (see Supporting Information).[15] The relative configurations of pyrrolidines **4, 6, 8** and **10** were assigned by analogy and by *nOe* experiments. Upon changing the nitrogen protecting group from tosyl (Ts) or *p*-methoxybenzenesulfonyl (PMBS) to 4-nitrophenyl sulfonyl (Ns), there was a slight decrease in the yield, but a high level of stereocontrol was still observed (Table 2, entry 6). The Ns group is usually more easy to remove.[16] γ-Substituted 4-pentenyl sulfonamides **13** and **16** gave only moderate selectivity (3:1 for **13** and 2:1 for **16**) favoring the *trans* pyrrolidine adducts (Table 2, entries **7** and **8**). Little difference between the electron-donating OMe and electron-withdrawing CF_3 benzyl substituents was observed. The relative configurations of the *cis* and *trans* isomers were assigned by X-ray crystallography and *nOe* experiments (see Supporting Information). The *trans* pyrrolidine is presumably favored due to equatorial placement of the γ-substituent in the cyclic transition state (see Supporting Information). It was not clear if substrate **19**, with an internal disubstituted olefin, would favor aminooxygenation (**20**) or oxidative amination (**21**). In the carboamination series[13a] only **21** was obtained. To our delight, the aminooxygenation product **20** was isolated as the major product with >20:1 diastereoselectivity and 7:1 aminooxygenation:oxidative amination selectivity. The stereochemistry of **20** was determined by X-ray crystallography (see Supporting Information).[15]

The mechanism illustrated in Scheme 2 provides a rationalization for the high degree of *cis* stereoselectivity observed in the aminooxygenation reaction of the α substituted substrates. It was reasoned that this reaction underwent a mechanism similar to the copper(II) promoted intramolecular carboamination reaction.[13a] The first C–N bond is proposed to form in a stereoselective manner *via syn* aminocupration through the chair-like transition state **23** or possibly the boat-like transition state **24**, generating an unstable organocopper(II) species **25**. This organocopper(II) species then undergoes homolysis, forming a primary carbon radical intermediate which is trapped by the TEMPO radical,[11f, 13] forming the *cis* aminooxygenation product **2**.

To demonstrate the synthetic utility of the method, we performed a short and efficient formal synthesis of (+)-monomorine (**28**). (+)-Monomorine is an indolizidine alkaloid that is known to be a trail pheromone of a health hazard pharaoh ant *Monomorium pharaonis L*.[17] Along with the other indolizidine alkaloids, (+)-monomorine has been the target of many organic chemists for some time. As a result, a number of different ways of synthesizing it have been reported.[18] Particularly relevant to this study was the synthesis reported by Bäckvall and co-workers[19] wherein they used aldehyde **27** as an intermediate in their synthesis of (+)-monomorine. Utilizing our method, aldehyde **27** was synthesized in 6 steps and 40% overall yield. Our route to **27** is 3 steps shorter than Bäckvall's approach. The 2,5-*cis*-pyrrolidine **8** was formed from substrate **7** in 94% yield and high selectivity (>20:1) (Table 2, entry 4). Substrate **7** was readily synthesized from commercially available D-norleucine (see Supporting Information). The TEMPO adduct **8** was oxidized to aldehyde **27** using *m*CPBA in 68% yield (Scheme 3).[20] We have previously also demonstrated that dissolving metal reduction can chemoselectively reveal one or both of the free amine and free alcohol functionalities.[11f]

On the basis of the proposed transition state for the α substituted 4-pentenyl sulfonamides (Scheme 2), we predicted that if the N-substituent was directly tethered to the α-carbon (e.g., substrate **29**), the reaction would occur *via* transition state **30**, which places the α-substitutent in a pseudoequatorial position, thereby favoring the formation of the 2,5-*trans* pyrrolidine adduct (Scheme 4). When sulfonamide **29** was subjected to the optimized reaction conditions for this copper(II) promoted aminooxygenation, it produced the *trans* pyrrolidine **31** in poor yield but with high diastereoselectivity (>20:1). We hypothesized that addition of excess TEMPO (3 equiv) caused the decomposition of the starting material *via* benzylic oxidation. When the amount of TEMPO was decreased to 1.5 equivalents, we were able to increase the

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yield to 59% with the same level of selectivity. The *trans* configuration of pyrrolidines **31** was confirmed by X-ray crystallography (Figure 1).[15] We have previously demonstrated that the SO_2 moiety in sultams such as **31** can be removed by dissolving metal reduction.[13a, 21]

In conclusion, we have developed a high yielding route for the synthesis of disubstituted pyrrolidines *via* the intramolecular copper promoted aminooxygenation of alkenes. These reactions afford the 2,3-*trans*-pyrrolidines in moderate selectivity and both the 2,5-*cis*- and 2,5-*trans*-pyrrolidines in excellent diastereoselectivity. The efficiency of this approach was demonstrated with the formal synthesis of (+)-monomorine. More efforts to apply this method to the total synthesis of interesting biologically active nitrogen heterocycles and further investigations into substrate scope and catalytic methods are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. CCDC 696031 (**2**), 711960 (**17**), 714177 (**20**) and 704323 (**31**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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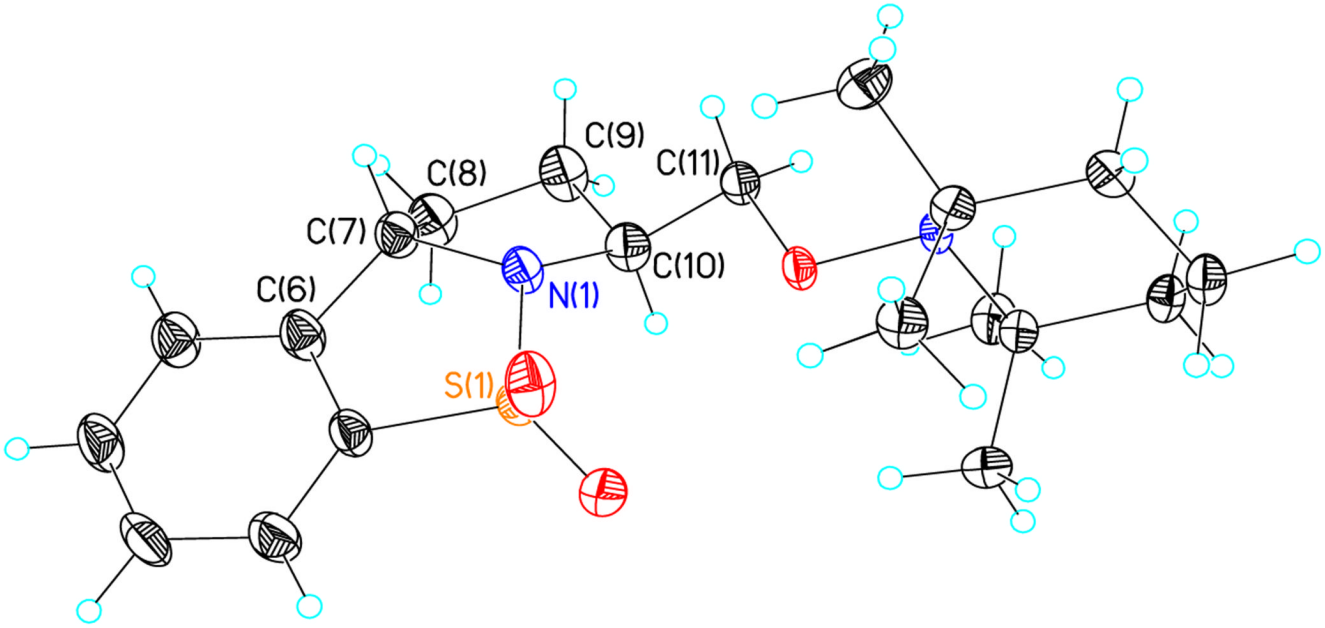

Figure 1.
Crystal structure of **31**.

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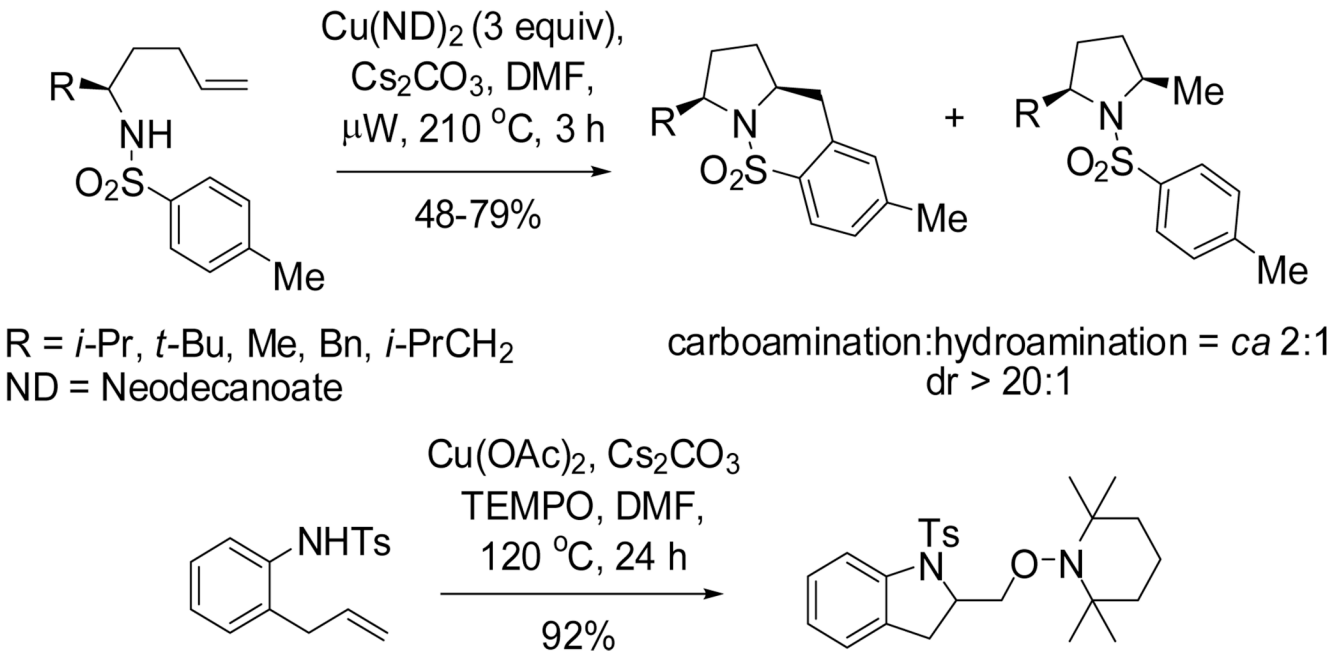

Scheme 1.
Copper(II) promoted diastereoselective formation of 2,5-*cis*-pyrrolidines and TEMPO trapping of radical intermediate.

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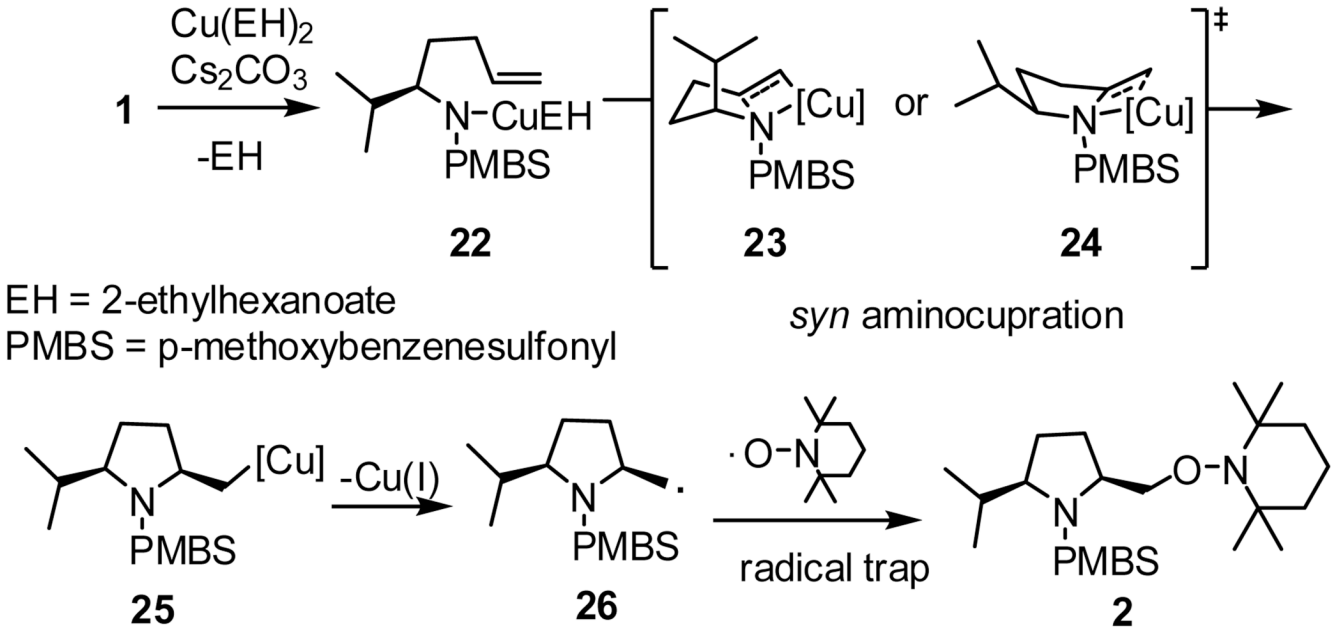

Scheme 2.
Proposed mechanism for the formation of 2,5-*cis*-pyrrolidine.

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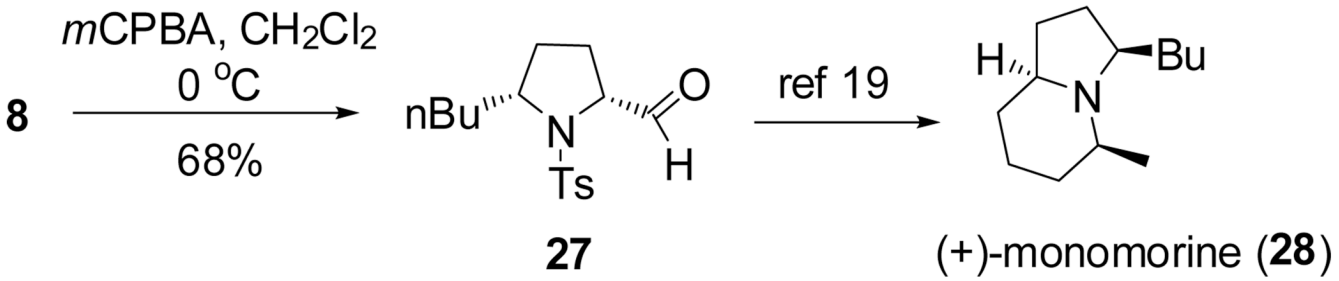

Scheme 3.
Formal synthesis of (+)-monomorine.

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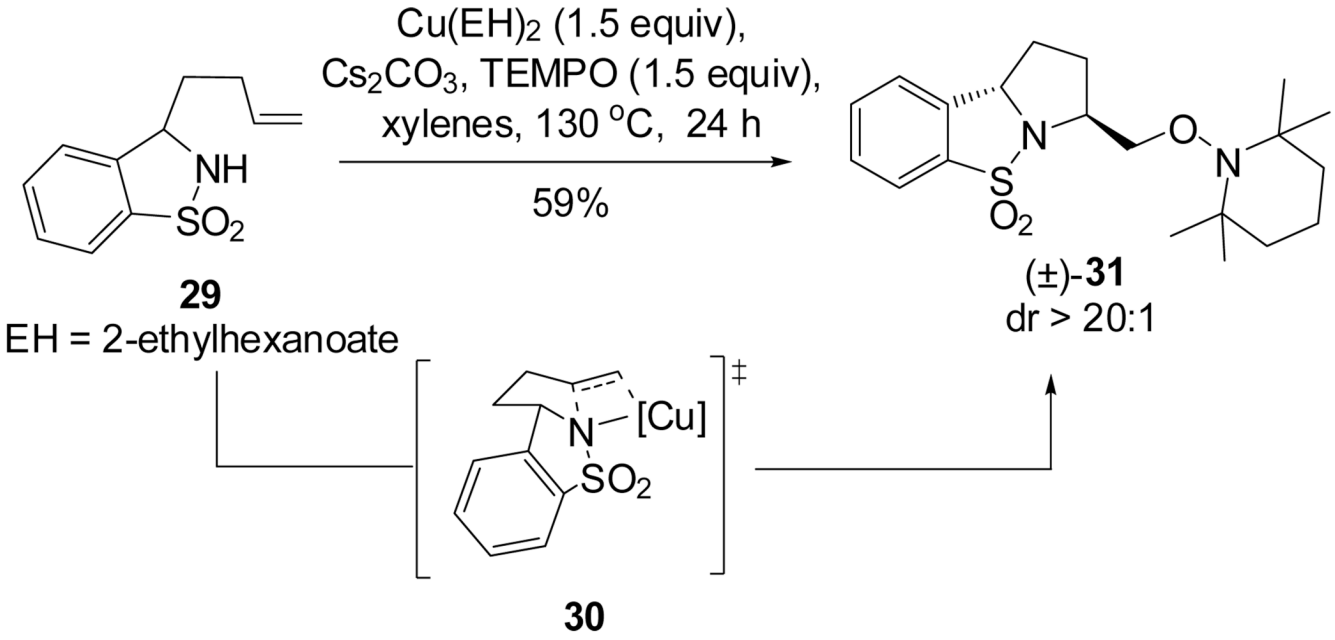

Scheme 4.
Diastereoselective aminooxygenation of sulfonamide **29** forming the *trans* pyrrolidine **31**.

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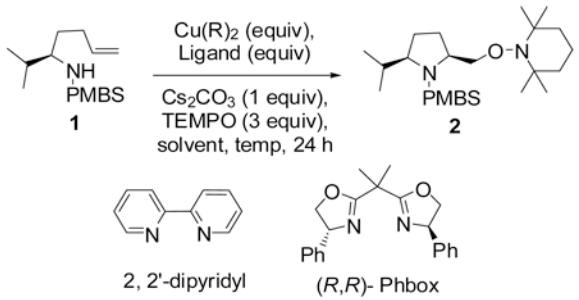
Table 1

Effects of varying the amount of $Cu(R)_2$, ligand, temperature and solvent.[a]



entry	R (equiv)	ligand (equiv)	solvent	temp (°C)	yield (%)[b]
1[c]	OTf (0.2)	2,2'-dipyridyl (0.2)	xylenes	130	20[d]
2[c]	OTf (0.2)	(*R*,*R*)-Phbox (0.2)	xylenes	130	60[d]
3	EH (3)	-	DMF	160	80
4	EH (1.5)	-	DMF	160	40
5	EH (1.5)	-	xylenes	130	94
6[e]	EH(1.5)	-	xylenes	130	78
7	EH (1.5)	-	xylenes	120	54[d]
8	EH (1.5)	-	DMF	130	40[d]
9	EH (1.5)	-	CF_3Ph	120	63[d]
10	EH (1.0)	-	CF_3Ph	120	38[d]
11	EH (1.0)	-	xylenes	130	68[d]

[a] All reactions were run in pressure tubes at 0.1 M w/r to **1**.

[b] Yield refers to amount of product isolated after purification by flash chromatography on silica gel.

[c] The reaction was run under O_2 (1 atm).

[d] The remainder of the material is the starting olefin **1**.

[e] The reaction was run using 1.5 equiv of TEMPO. EH = 2-ethylhexanoate, PMBS = *p*-methoxybenzenesulfonyl

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Table 2

Diastereoselective aminooxygenation of alkenes.[a]

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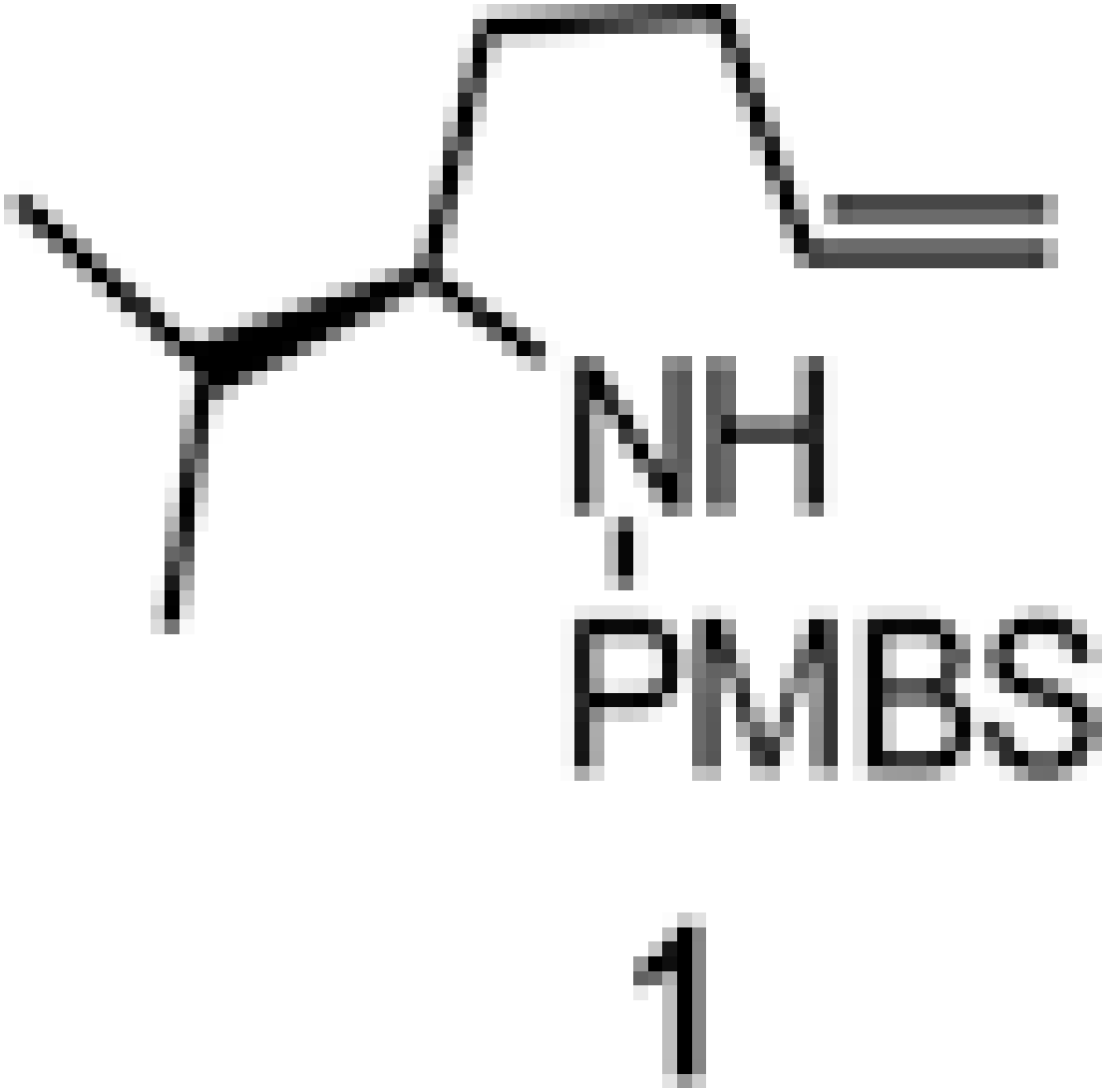
1	 **1**

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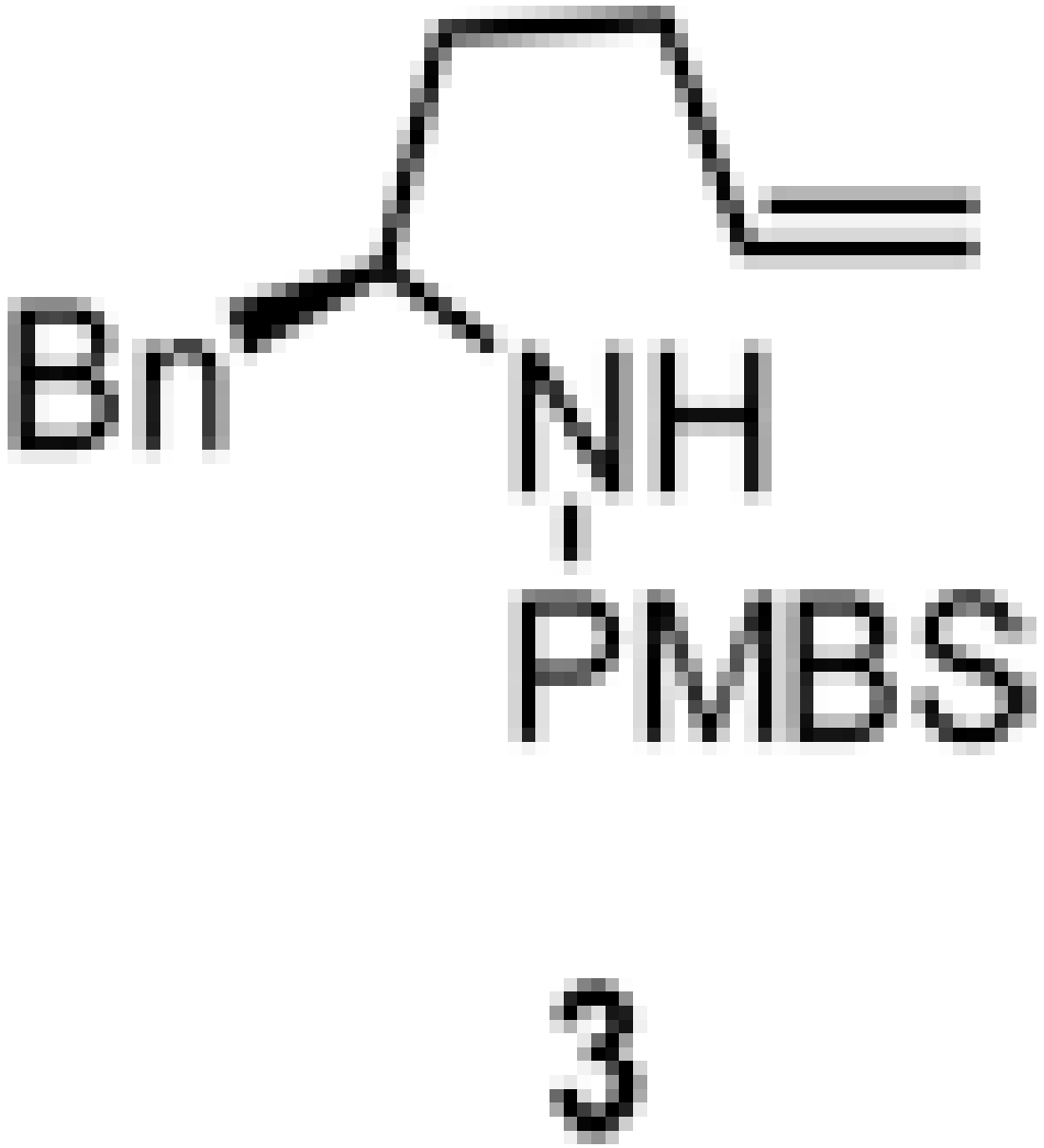
2	

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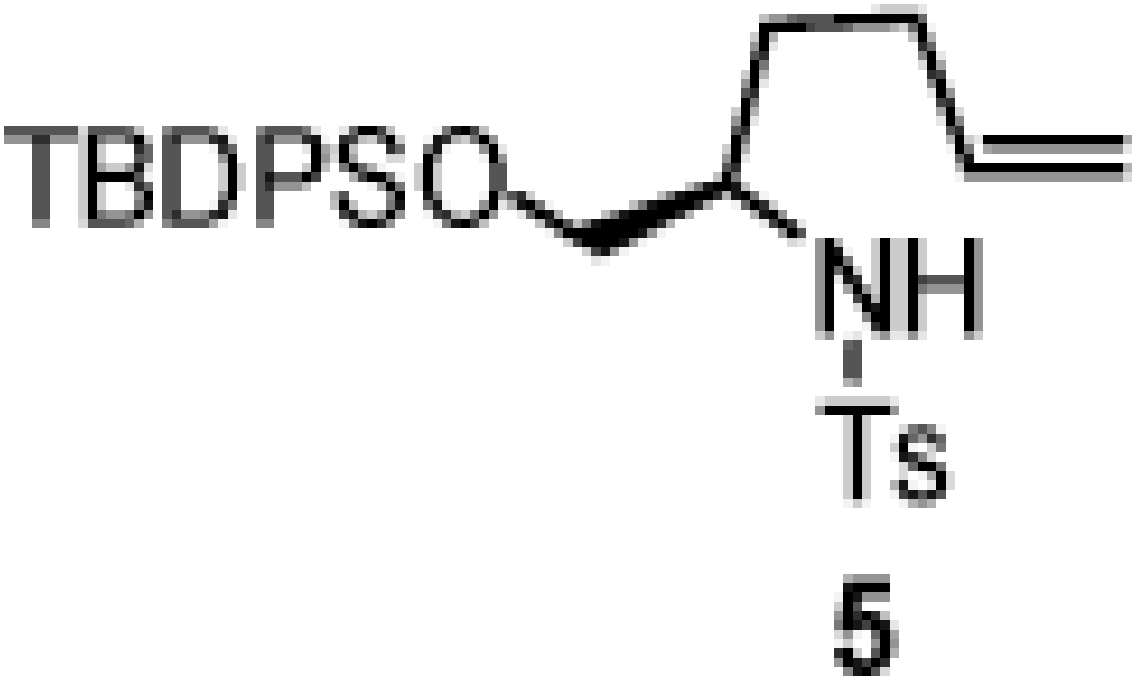
entry	substrate
3	

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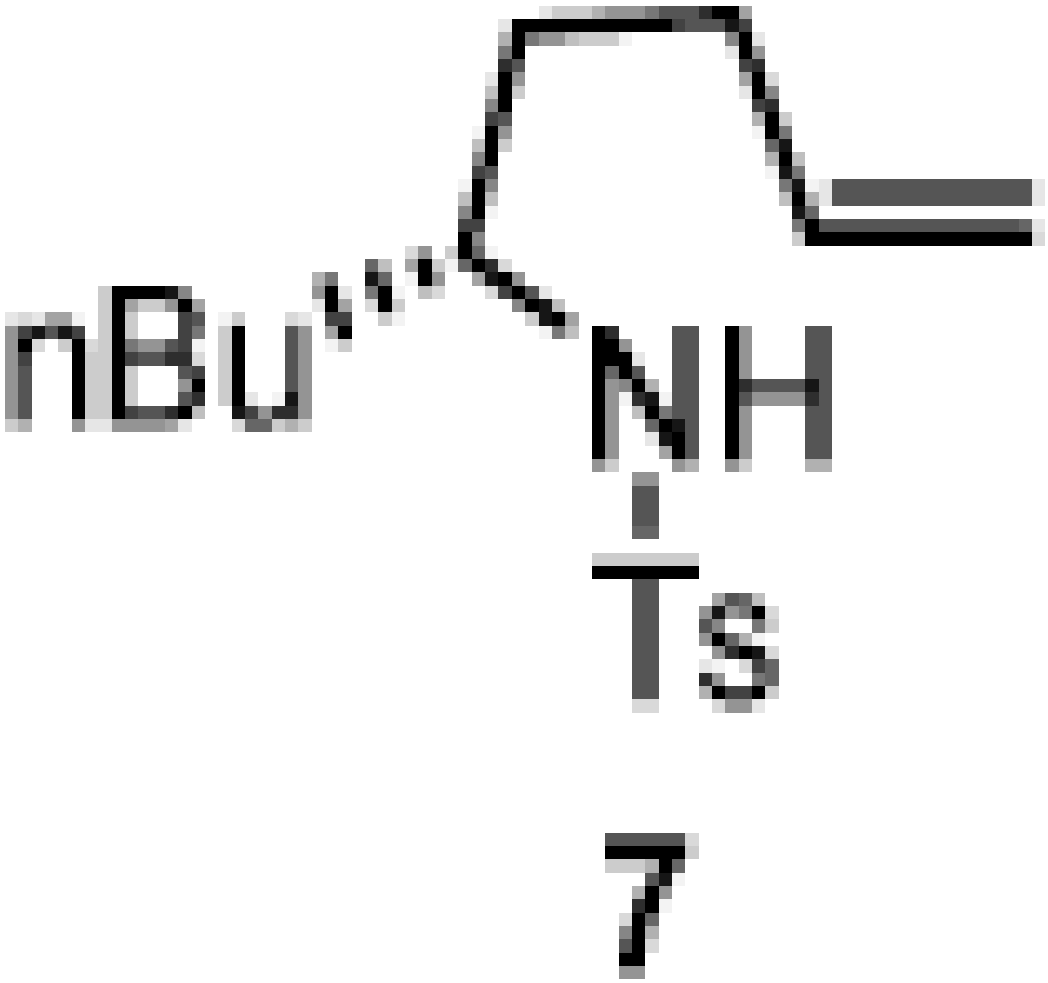
entry	substrate
4	

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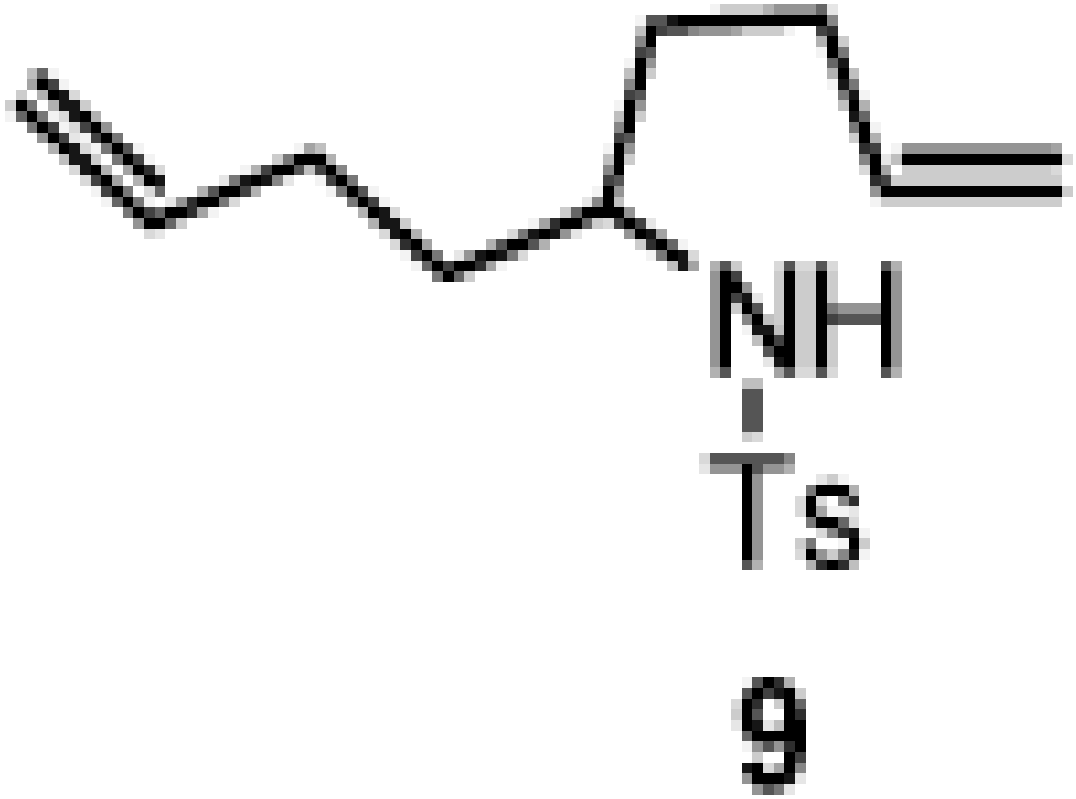
entry	substrate
5	

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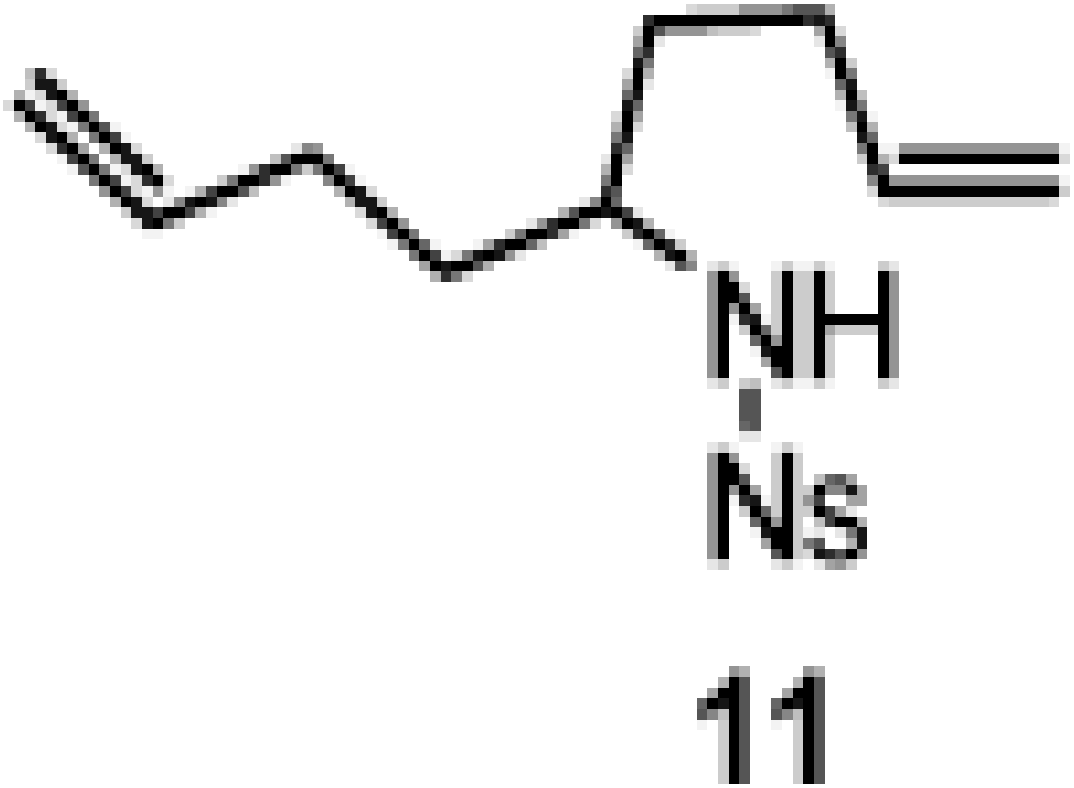
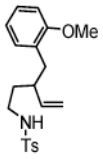
entry	substrate
6	 **11**
7	 **13**

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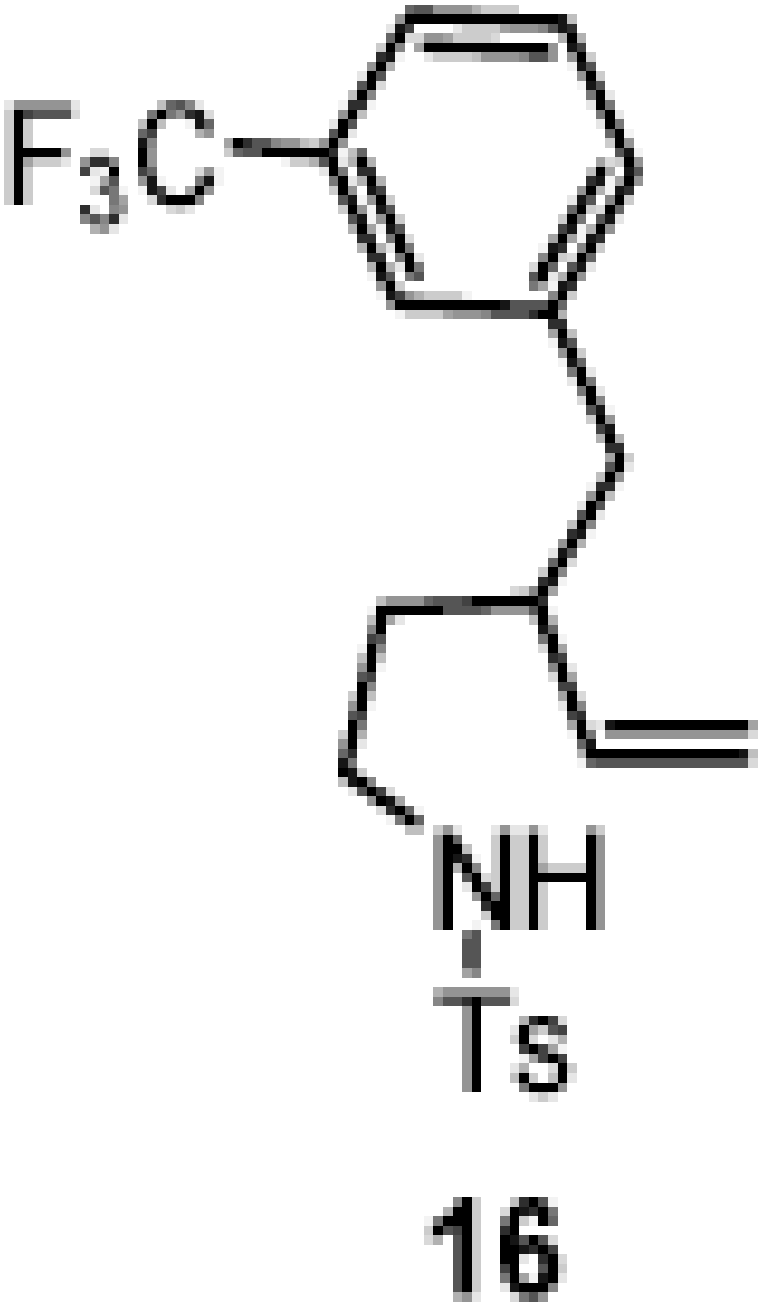
entry	substrate
8	

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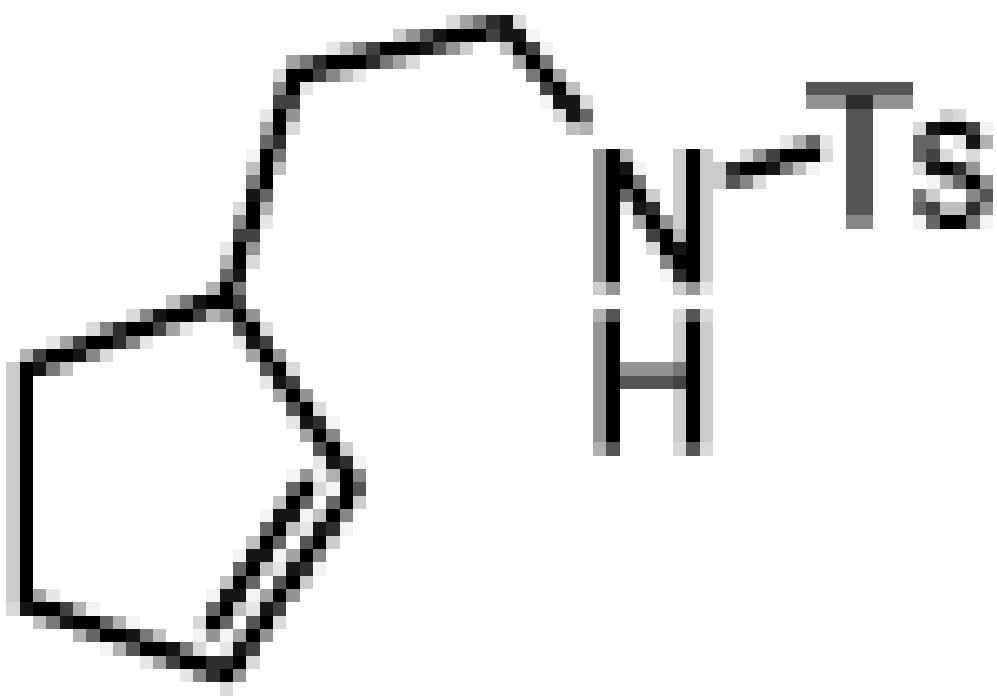
entry	substrate
9[e]	

19

R = 2,2,6,6-tetramethylpiperidine

[a] Reaction conditions: 1.5 equiv of $Cu(EH)_2$, 3 equiv of TEMPO, 1 equiv of Cs_2CO_3, xylenes (0.1 M), 130 °C, 24 h, pressure tube.

[b] Yield refers to amount of product isolated upon purification by column chromatography on SiO_2.

[c] Yield refers to the sum of the products isolated by chromatography on SiO_2.

[d] Diastereomeric ratio was determined by analysis of the crude ^1H NMR spectrum.

[e] The reaction was run at 140 °C.

[f]Yield refers to amount of **20** isolated.

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